Southern Medical Journal

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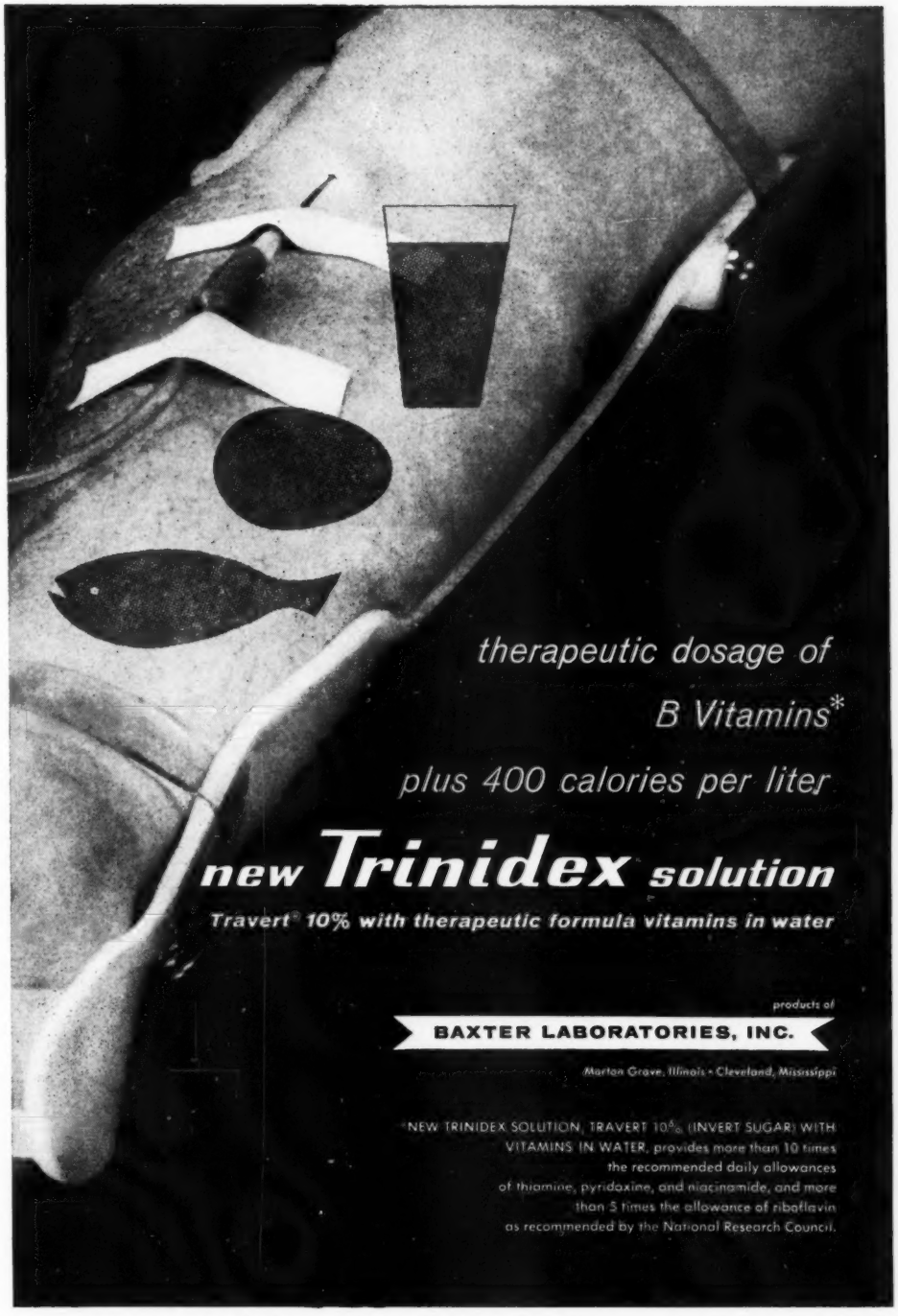
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Bibliography

1. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955. 2. Davis, C. H.: Am. J. Obst. & Gynec. 68:559 (Aug.) 1954. 3. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 4. Davis, C. H.: J.A.M.A. 92:306 (Jan. 26) 1929.

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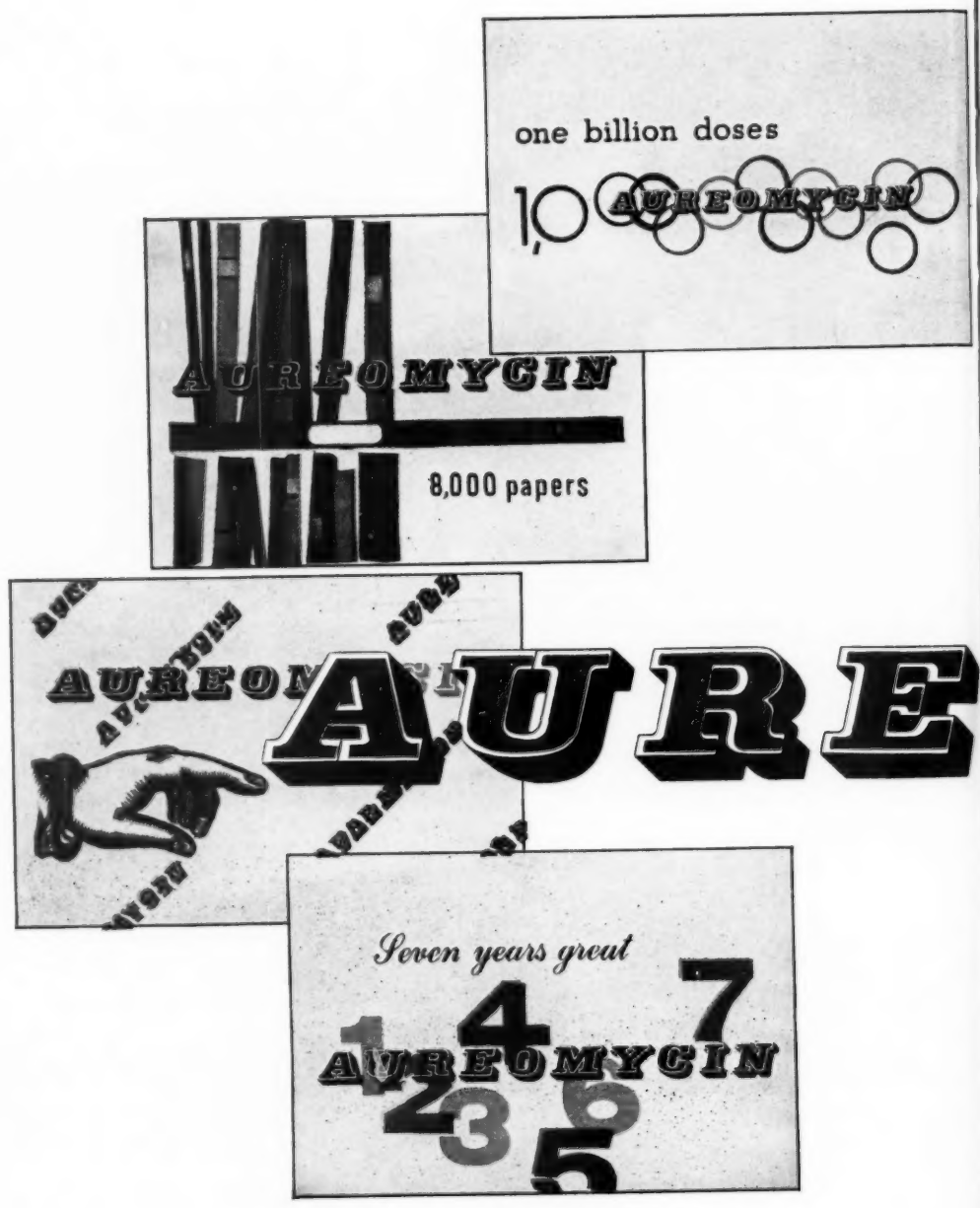
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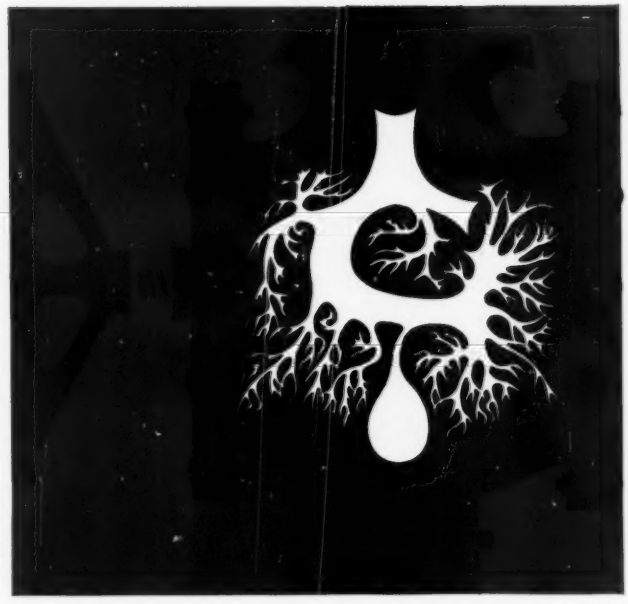

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PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc. for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

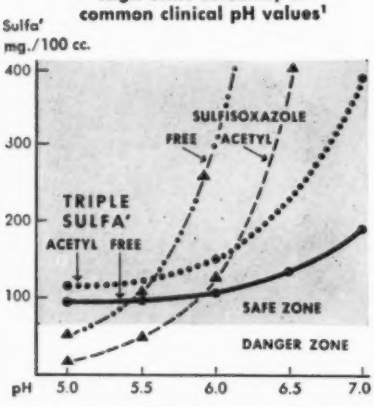
SHARP & DOHME
PHILADELPHIA 1, PA.
DIVISION OF MERCK & CO., INC.

REFERENCE: 1. Kirwin, T. J., Lowsley, O. S., and Menning, J.: Am. J. Surg. 62:330-335, December, 1943.

a sulfonamide preparation with

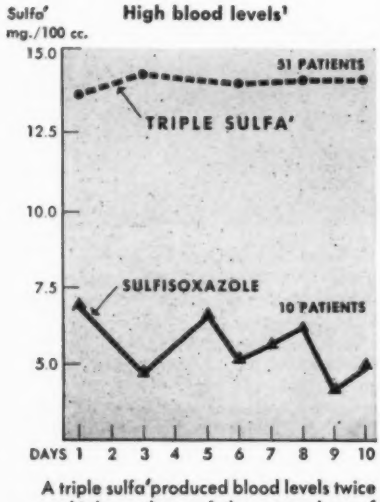
"maximum therapeutic efficiency at a minimum risk to the patient..."[1]

High urine solubility at common clinical pH values[1]



A triple sulfa' has better solubility at the acidic reactions of urine in many patients.[1] (Chart adapted).

High blood levels[1]



A triple sulfa' produced blood levels twice as high as those of the same dose of sulfisoxazole (6 Gm. per day).[1] (Chart adapted).

Tripazine*

Brand of meth-dia-mer sulfonamides

TRIPLE SULFONAMIDE TABLETS

Triple sulfonamide mixtures such as Tripazine are "preparations of choice" for treatment of sulfonamide-sensitive infections. "High blood levels and excellent tissue diffusion can thus be combined with a few sensitization reactions and reliable protection of the kidney."[1]

Tripazine is highly useful in

- Systemic or localized infections, particularly those caused by hemolytic streptococci (Lancefield's Group A) • pneumococci • micrococci (staph.) • meningococci • Klebsiella pneumoniae • Hemophilus influenzae • Neisseria gonorrhoeae

- in such diseases as
  nonviral pneumonia • bacillary dysentery • urinary tract infections • meningococcic bacteremia and meningitis • gonococcic urethritis • and in conjunction with an antibiotic in actinomycosis and gas gangrene

- for prophylaxis of
  rheumatic fever • meningococcal and streptococcal infections • bacillary dysentery during epidemics

Each scored, gray Tripazine tablet supplies the closely related sulfonamides: sulfadiazine, sulfamerazine, sulfamethazine, 0.167 Gm. each.

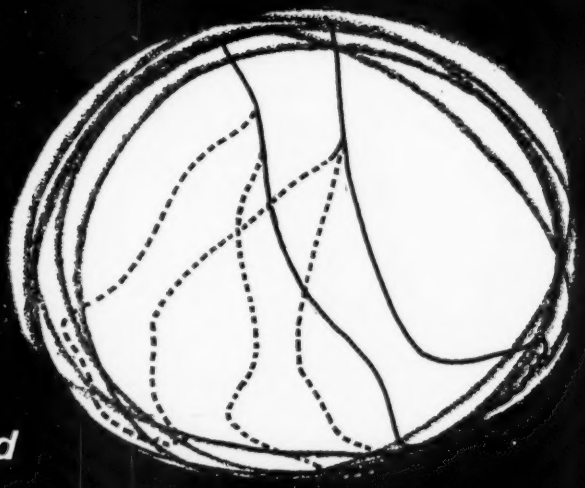
0.5 Gm. tablets, in bottles of 100 and 1000.

1. Lehr, D.: Present Status of Sulfonamide Therapy, Mod. Med. **23**:111 (Jan. 15) 1955

*Trademark

EATON LABORATORIES

NORWICH • NEW YORK



range of motion
rapidly increased

in Rheumatoid Arthritis

Sterane*

the most potent anti-arthritic

3 to 5 times more potent than hydrocortisone or cortisone

notably free of major hormonal side effects such as edema due to sodium and water retention, hypopotassemia, and hypertension

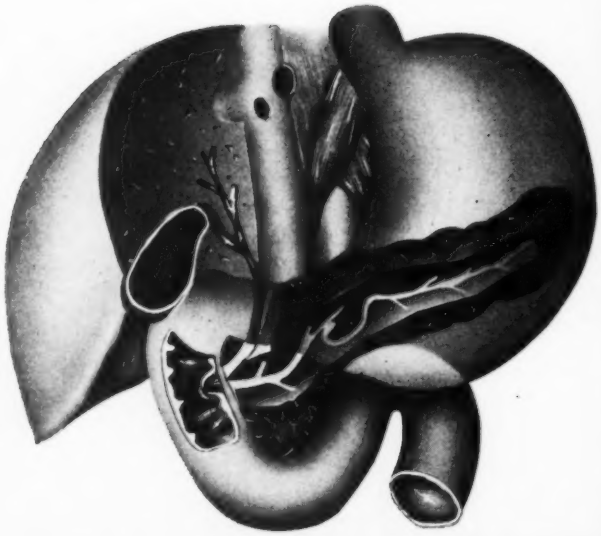
seldom requires low-sodium diets or potassium supplements in patients without cardiac complications when given in usual therapeutic dosage

preliminary findings,[1] based on the measuring of pituitary ACTH suppression potency of various corticoids, appear to indicate that STERANE is 20% more potent than the cortisone analog, prednisone

supplied: in white, scored 5 mg. tablets in the familiar Pfizer oval shape. Bottles of 20 and 100.

1. Forsham, P. H., et al.: Paper presented at First Internat. Conf. on Prednisone and Prednisolone, New York, N. Y., May 31-June 1, 1955.

PFIZER LABORATORIES *Division Chas. Pfizer & Co., Inc. Brooklyn 6, New York*



constipation
and
related
functional
G. I. distress

markedly relieved in
8 out of 10 patients*
by inexpensive, physiologic
stimulant

DECHOLIN® with Belladonna

improved liver function PLUS *reliable spasmolysis*

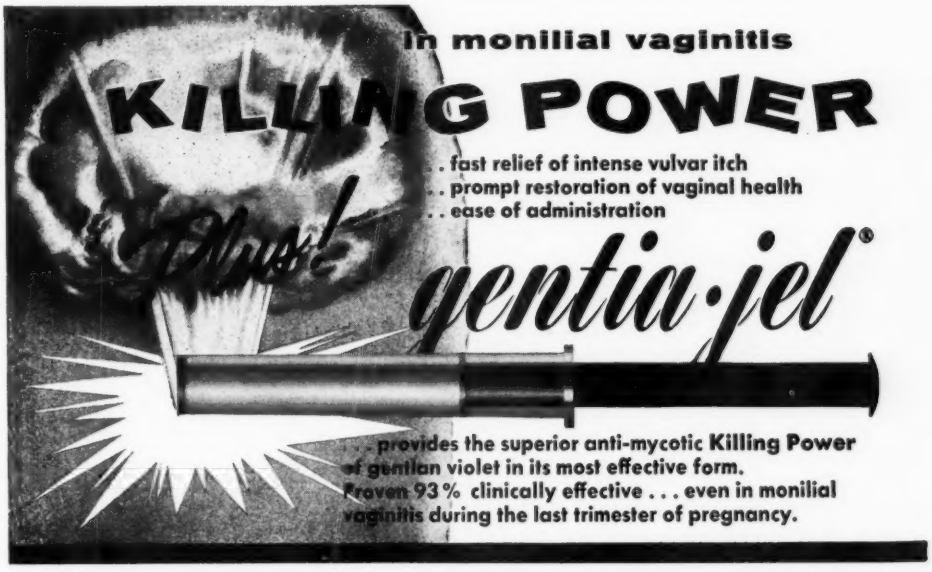
Steps up flow of dilute bile by *hydro*choleresis • physiologic elimination without catharsis • relieves spasm • no cramping • no evidence of tolerance • helps establish normal bowel habits

One or, if necessary, two *Decholin*/Belladonna Tablets t.i.d. gives your patients more effective relief of constipation and related G.I. complaints: flatulence, bloating, belching, nausea and indigestion.

Each tablet contains *Decholin* (dehydrocholic acid, *Ames*) 3¾ gr., and extract of belladonna ⅙ gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100 and 500.

*King, J. C.: Am. J. Digest. Dis. *22*:102, April, 1955.

AMES
COMPANY, INC • ELKHART, INDIANA • Ames Company of Canada, Ltd., Toronto


In monilial vaginitis
KILLING POWER
. . fast relief of intense vulvar itch
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. . ease of administration
Plus!
gentia·jel®
. . provides the superior anti-mycotic Killing Power of gentian violet in its most effective form.
Proven 93% clinically effective . . . even in monilial vaginitis during the last trimester of pregnancy.

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PEN·VEE·*Oral**

Penicillin V, Crystalline (Phenoxymethyl Penicillin)

the totally new penicillin for decisive oral dependability

Supplied: Tablets, 125 mg. (200,000 units), bottles of 36. Also available: Tablets BICILLIN®-VEE, 100 mg. (100,000 units) of benzathine penicillin G and 62.5 mg. (100,000 units) of penicillin V, bottles of 36.

Wyeth
Philadelphia, Pa.

*Trademark

After 20 Years — Still

The Nasal Medication of Choice

of many PHYSICIANS and their

PATIENTS

Both

CHILDREN

and

ADULTS

Why RHINALL Contains NO Antibiotic

The nose is lined with ciliated epithelium with an overlying **moving** blanket of mucus that clears the nose of foreign matter every 10 minutes.

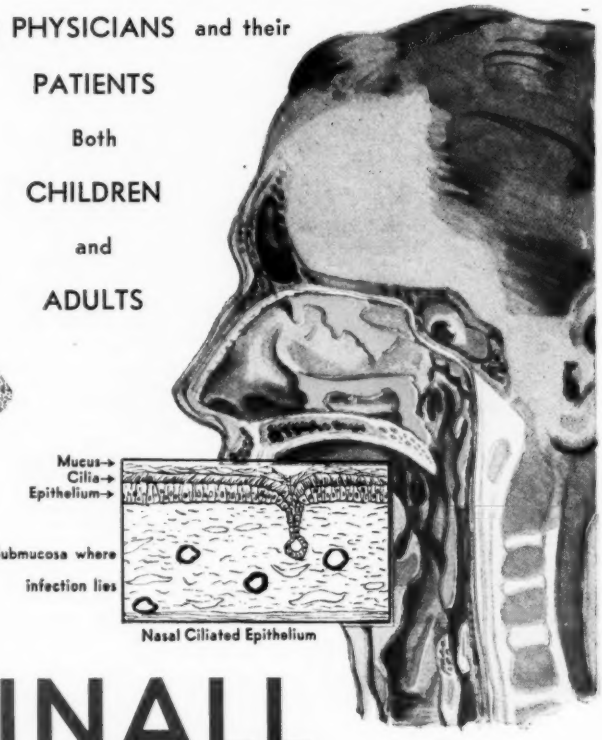
The **'common cold'** is caused by a virus infection for which we have no effective medication.

When secondary infection occurs, the offending bacteria are within the membrane — not on the surface.

Medication applied locally is partly diluted and partly carried out by the moving blanket of mucus.

Antibiotics must reach the submucosa in sufficient concentration and stay in contact with the offending bacteria a sufficient length of time to be effective . . . and the **risk of sensitization** is always present.

VENTILATION and DRAINAGE
(Vaso-Constriction) (Stimulation of Cilia)
the 'SINE QUA NON' of Nasal Therapy



Nasal Ciliated Epithelium

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NOSE DROPS

1-oz. Bottle with Dropper

★ EFFECTIVE
★ PLEASANT TO USE
★ NO AFTER REACTION
★ NO RISK OF SENSITIZATION

Ethical Specialties for the Profession
Samples on Request

RHINOPTO COMPANY
Dallas
Manufacturers of
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. . . and for Convenience
½-oz. Plastic Spray Bottle

METANDREN® LINGUETS®

the most potent oral androgen

FEMANDREN® LINGUETS®

the most potent oral estrogen with the most potent oral androgen

Buccally or sublingually absorbed LINGUETS by-pass liver inactivation or gastric destruction—are virtually as potent as parenteral steroids—provide effective, convenient, low-cost hormone therapy.

Supply: Metandren Linguets, 5 mg. (white, scored) and 10 mg. (yellow, scored). Femandren Linguets (green, scored), each containing 0.02 mg. ethinyl estradiol and 5 mg. methyltestosterone.

Metandren® (methyltestosterone U.S.P. CIBA)
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C I B A Summit, N. J.

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...instantaneous anesthesia

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Propoxycaine Hydrochloride

*TRADEMARK OF GEORGE A. BREON & COMPANY

...prolonged anesthesia

First choice for nerve block and infiltration anesthesia

...low irritation potential

...minimal toxicity

...no vasoconstrictor needed

Supplied: 0.5%, 5 mg. BLOCKAIN per cc., vials of 30 cc. $2.00 per vial.

PROOF AT NO COST send me postpaid *1 vial* with this order for 6 vials. Bill me later. However, I may return the 6 unused vials for cash refund if not completely satisfied.

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Penicillin V, Crystalline (Phenoxymethyl Penicillin)

the totally new penicillin

for decisive oral dependability

Supplied: Tablets, 125 mg. (200,000 units), bottles of 36. Also available: Tablets BICILLIN®-VEE, 100 mg. (100,000 units) of benzathine penicillin G and 62.5 mg. (100,000 units) of penicillin V, bottles of 36.

Wyeth

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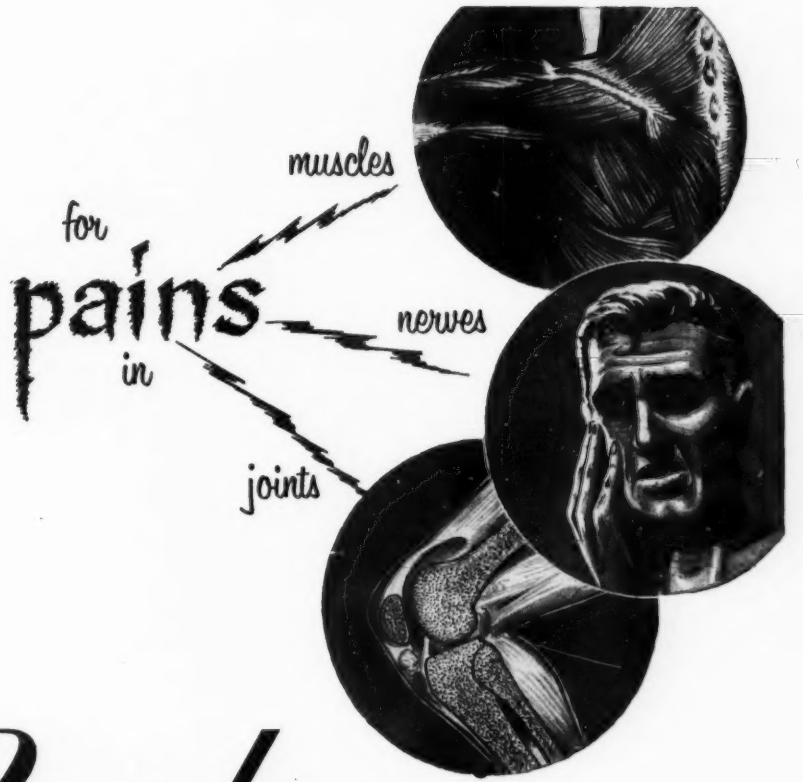

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a strong local analgesic and non-irritating counterirritant for relief of pain in neuralgia, muscular rheumatism and in muscular aches and strains.

Containing 58% salicylates (methyl salicylate and aspirin), with menthol and camphor, in an alcohol-oil base, Panalgesic provides prompt relief of muscle, nerve, or joint pains. A green liquid, Panalgesic is virtually non-greasy and does not stain the clothing. Panalgesic is issued in 2-ounce bottles and in half-gallon dispensing bottles.

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here's a good long lift when a lift is needed...

the NEW psycho-normalizer

AMBAR® EXTENTABS

Ambar Extentabs and Tablets contain, in intermediate dosage, the potent CNS stimulant, methamphetamine, plus phenobarbital. Combined in an optimal ratio of 6.5 parts phenobarbital to 1 part methamphetamine, methamphetamine's potent stimulating influence is firmly controlled, resulting in a gentle, "jolt-free" normalization of depressed moods and excessive appetite.

normalize the depressed mood, suppress the urge to overeat

How Ambar Extentabs work a 12-hour day... without time off for getting started. Each Extentab is equivalent to 3 full doses in one tablet. Dose number one, present in the tablet coating, is released quickly yet smoothly. Needed clinical effect is promptly achieved.

without time out for dosage breaks. Extentab-contained doses two and three are distributed throughout a special, Robins-developed extended-release core. Clinical effect is uniformly maintained without interruptions for dosage breaks.

Ambar Extentabs —
Methamphetamine hydrochloride 10.0 mg.
Phenobarbital (1 gr.) . . . . . 64.8 mg.
Average duration of therapeutic effects 10-12 hours

Ambar Tablets —
Methamphetamine hydrochloride 3.33 mg.
Phenobarbital (1/3 gr.) . . . . . 21.6 mg.
Average duration of therapeutic effects 4 hours.

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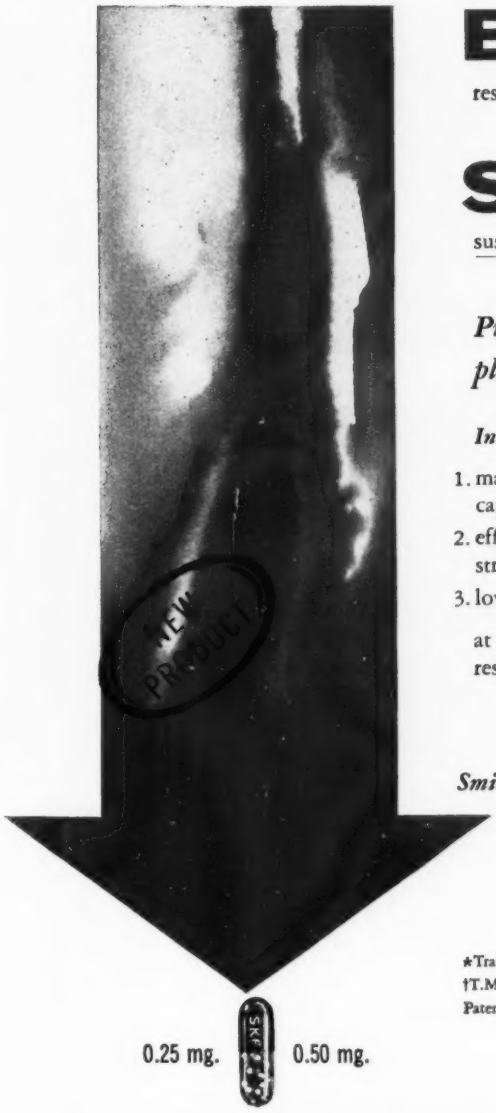
Announcing: the newest advance in reserpine therapy



Eskaserp*

reserpine, S.K.F.

Spansule†

sustained release capsules, S.K.F.

Prolonged control of blood pressure, plus gentle long-lasting sedation

Investigators report these advantages:

1. maximum patient convenience—a single 'Spansule' capsule q12h insures 24-hour uninterrupted effect;
2. effective therapy with either of two low dosage strengths—0.25 mg. and 0.50 mg.;
3. low incidence of side effects;

at no increase in cost over conventional reserpine therapy.

Smith, Kline & French Laboratories, Philadelphia

0.25 mg. 0.50 mg.

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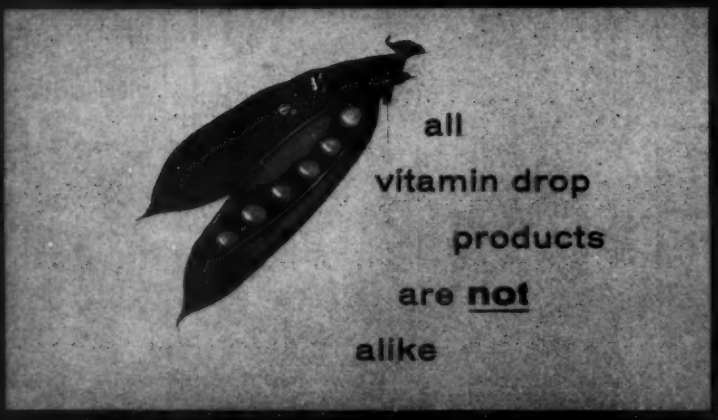
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.
Patent Applied For.



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is "naturally" superior because...

natural vitamin A with all known and fully utilizable active isomers—as compared to synthetic vitamin A which affords only one isomer which requires conversion in the body before it can be utilized in the visual process.

natural vitamin D complex for superior protection against rickets as compared, unit for unit, with synthetic vitamin D.

aqueous vitamins A and D for far faster and more complete absorption and utilization as compared with oily solutions.

no fish oil, no fish taste, no regurgitation.

costs no more, so why not give the greater protection of Vi-Syneral Vitamin Drops (natural vitamins A and D, made aqueous, B complex factors, ascorbic acid).

bottles of 15 cc., 30 cc., and package of 45 cc.

SAMPLES from

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Mysteclin

STECLIN-MYCOSTATIN
SQUIBB TETRACYCLINE-NYSTATIN

WELL TOLERATED BROAD SPECTRUM ANTIBACTERIAL THERAPY PLUS ANTIFUNGAL PROPHYLAXIS

BROAD SPECTRUM ANTIBIOTIC THERAPY,
EFFECTIVE IN MANY COMMON INFECTIONS

Because it contains Steclin (Squibb Tetracycline), MYSTECLIN is an effective therapeutic agent for most bacterial infections. When caused by tetracycline-susceptible organisms, the following infections are a few of those which can be expected to respond to MYSTECLIN therapy:

bronchitis	gonorrhea	osteomyelitis	pyelonephritis
colitis	lymphadenitis	otitis media	sinusitis
furunculosis	meningitis	pneumonia	tonsillitis

MYSTECLIN is also indicated in certain viral infections and in amebic dysentery.

BROAD SPECTRUM ANTIBIOTIC THERAPY,
WITH A MINIMUM OF SIDE EFFECTS

In clinical use, Steclin has produced an extremely low incidence of the gastrointestinal distress sometimes observed with other broad spectrum antibiotics. Mycostatin (Squibb Nystatin), as contained in MYSTECLIN, is also a particularly well tolerated antibiotic and has produced no allergic reactions, even after prolonged administration.

BROAD SPECTRUM ANTIBIOTIC THERAPY,
WITHOUT THE DANGER OF MONILIAL OVERGROWTH

Because it contains Mycostatin, the first safe antifungal antibiotic, MYSTECLIN effectively prevents the overgrowth of Candida albicans (monilia) frequently associated with the administration of ordinary broad spectrum antibiotics. This overgrowth may sometimes cause gastrointestinal distress, anal pruritus, vaginitis, and thrush; on occasion, it may have serious and even fatal consequences.

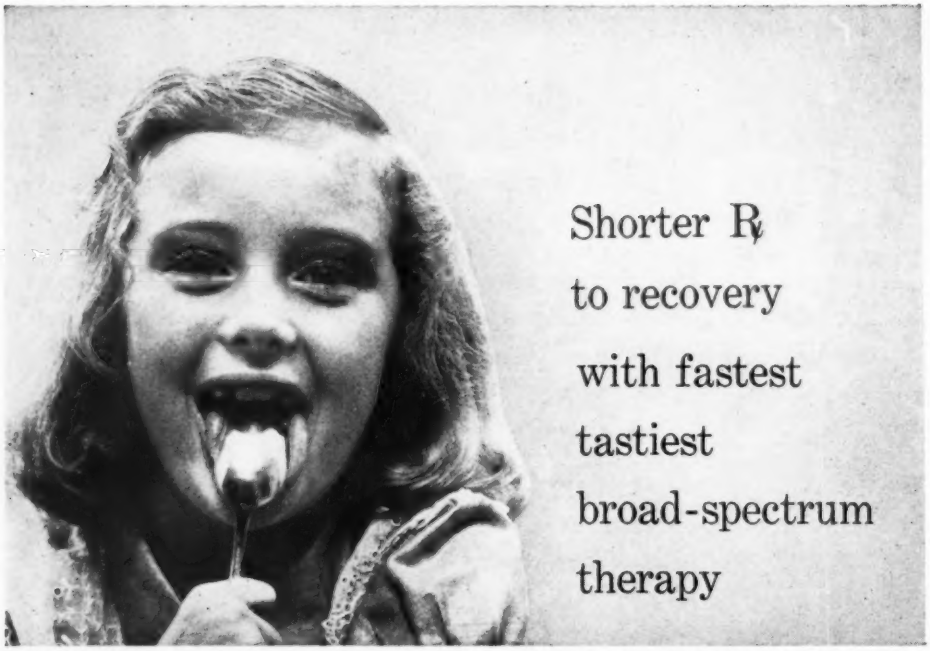
SQUIBB

Each MYSTECLIN capsule contains 250 mg. Steclin Hydrochloride and 250,000 units Mycostatin.

Minimum adult dose: 1 capsule q.i.d.

Supply: Bottles of 12 and 100.

"MYSTECLIN", "STECLIN" AND "MYCOSTATIN"® ARE SQUIBB TRADEMARKS



NEW palatability, **NEW** convenience, **NEW** versatility . . . the same unexcelled efficacy and toleration

TETRABON*

(unique fruit-flavor)

Brand of tetracycline

Supplied in 2 ounce bottles, containing 125 mg. tetracycline per 5 cc. teaspoonful.

TETRABON SF†

Brand of tetracycline hydrochloride with vitamins

(fruit-mint flavored)

Sugar free. Supplied in 2 ounce bottles, containing 125 mg. tetracycline per 5 cc. teaspoonful.

These new, remarkably palate-pleasing non-alcoholic homogenized mixtures of Pfizer-discovered tetracycline are now *standardized and ready-mixed* at Pfizer Laboratories for uniformity and reliability.

TETRABON SF supplies with each average daily dose of tetracycline the special vitamin formula recommended for the treatment of stress conditions, thus giving antibiotic therapy and metabolic support with a single prescription.

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NEW STANDARDS FOR TETRACYCLINE THERAPY IN NEW READY-MIXED LIQUID FORM

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Non-narcotic

cough specific—

Romilar 'Roche' is at least as effective as codeine in relieving cough -- but it does not constipate and is not habit-forming. 10 mg Romilar® equals 15 mg (1/4 gr) codeine. Romilar is available as a syrup, in tablets and as an expectorant.

More and more physicians —

...are prescribing Gantrisin® 'Roche.' Why? Because they've found that this single, soluble wide-spectrum sulfonamide is usually both effective and well tolerated. There are over 300 references to Gantrisin in recent medical literature.

Ménière's syndrome, cerebral arteriosclerosis, fenestration surgery, streptomycin toxicity

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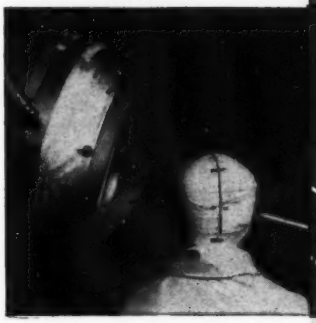

narcotization

motion sensitivity in every form of travel

effective
control of
nausea
vomiting
vertigo

associated with labyrinthine dysfunction

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Brand of meclizine hydrochloride

Two convenient dosage forms . . . tasteless TABLETS (25 mg.) and mint-flavored, universally acceptable CHEWING TABLETS (25 mg.). Bonamine is ethically promoted. *Trademark

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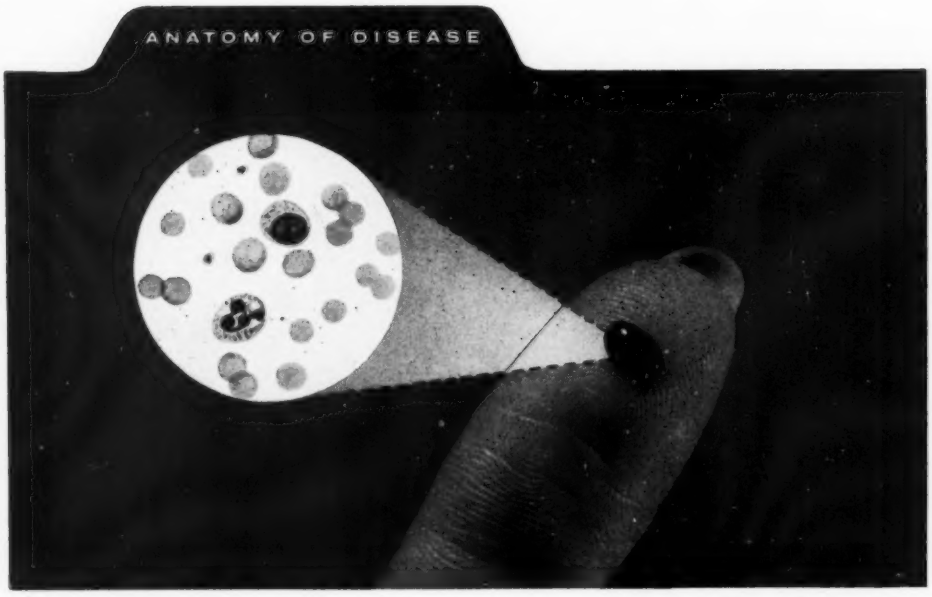

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for better patient response... use the latest development in antianemia therapy

ARMATRINSIC

- with new ferrous betaine hydrochloride... releases hydrochloric acid, important for proper iron absorption
- provides complete therapy for all treatable anemias

Just 1 Armatrinsic capsule b.i.d. supplies:

Vitamin B_{12} with Intrinsic factor Concentrate*	1 U.S.P. Unit (Oral)
Liver Fraction 2 N.F. with Duodenum (Containing Intrinsic factor)	100 mg.
Vitamin B_{12} Activity concentrate	10 mcg.
Ferrous Betainate HCl equivalent to: 100 mg. of Elemental Iron 18 cc. of N/10 HCl	666 mg.
Folic acid	1.4 mg.
Ascorbic acid U.S.P.	100 mg.
Cobalt Chloride	20 mg.
Molybdenum	1.5 mg.
Copper	0.50 mg.
Manganese	0.50 mg.
Zinc	0.50 mg.

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Adults: 2 or 3 capsules daily with meals
Bottles of 50 capsules (small, attractive, odorless)

AND WHEN A LIQUID HEMATINIC IS PREFERRED
PRESCRIBE **ARMATINIC®** *Liquid*
FOR A FAST START AND VIGOROUS IMPROVEMENT

Bottles of 8 and 16 fl.oz.

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A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

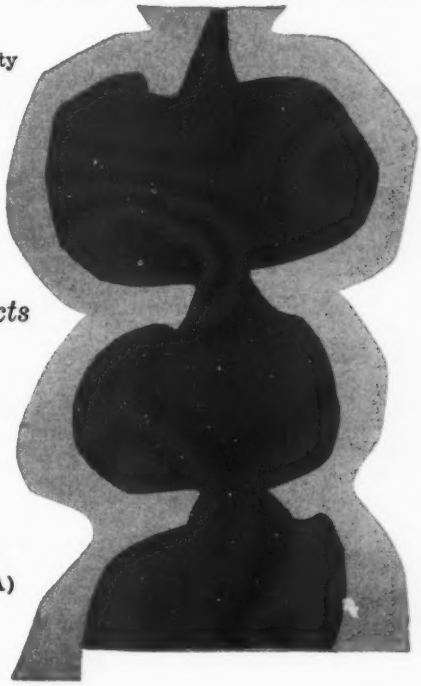
Trasentine® - Phenobarbital

- Inhibits Parasympathetic Activity
- Relaxes Smooth Muscle Directly
- Exerts Local Anesthetic Effect on G-I Mucosa
- Sedates the Patient

Without Atropine Side Effects

Each tablet contains 50 mg. Trasentine hydrochloride and 20 mg. phenobarbital.
Also available: Trasentine hydrochloride Tablets, 75 mg.

Trasentine® hydrochloride
(adiphenine hydrochloride CIBA)



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CIBA *Summit, N. J.*

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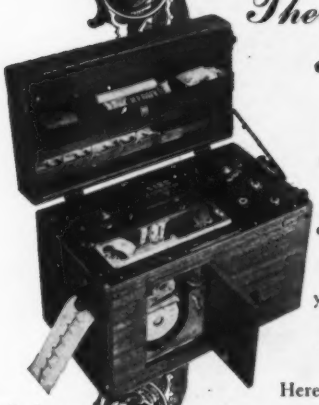
There can be "extra dividends" on an ECG *investment*



Sanborn Viso-Cardiette

If you are considering purchase of an electrocardiograph, it may seem to you that all makes are "pretty much alike", since none can do more for you clinically than produce an electrocardiogram. Looking at it from an investment point of view, you *expect* your instrument to pay you good dividends in the form of specific benefits to you and your patients. But, investments that pay *extra dividends* are the happy ones. Here are a few that go with Viso-Cardiette ownership.

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Initial thinking in considering an ECG should reach beyond favorable first impressions to the instrument's potential continuity of service. There the best yardstick is to inquire among those of your colleagues or associates who own electrocardiographs. You will soon learn that the name "SANBORN" is synonymous with "dependability", which is an understandable result of over 30 years of specialization in the design and manufacture of this type of precision instrument.

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There are many "extra dividends" in dealing directly with the maker of your ECG. The interest in and responsibility towards you as the user is with Sanborn Company instead of an intermediate source. There is a standardization of prices, and the cost is the same to all. Also, the Viso user can avail himself of direct contact with the designers of his instrument, and his local serviceman is, more likely than not, a SANBORN man, full-time and factory-trained.

EXCLUSIVE Service Helps

Every alternate month all Viso owners receive, free of charge, the Sanborn Technical Bulletin which contains much helpful data on operating procedure, maintenance, ideas and techniques developed by others, and the like — all prepared by an experienced staff. In addition, a five-part Sanborn Service Course by correspondence is available for technicians principally, who wish technical information a bit beyond the preliminary Instructions. No other ECG maker offers these "extra dividends" in Service.

Ask for details of a 15-day, no-obligation clinical test plan.

Sanborn Company

CAMBRIDGE 39, MASSACHUSETTS

To your hypercholesteremic patient with

CARDIOVASCULAR DISEASE, ANGINAL SYNDROME, DIABETES MELLITUS, OBESITY,

MONICHOL® means far more than a striking reduction in serum cholesterol levels

MONICHOL

- often produces an entirely new mental outlook characterized by an improvement in mood and a sense of euphoria.[1,2]
- relieves anginal pain.[2]
- produces objective and subjective improvement[2] in diabetic, obese hypercholesteremic patients.

1. Sherber, D.A., and Levitas, M.M.: J.A.M.A. 152:682 (June 20) 1953.
2. Albert, A., and Albert, M.: Texas State J. Med. 50:314 (Dec.) 1954.

IVC

IVES-CAMERON COMPANY
Philadelphia 1, Pa.

MONICHOL

(Polysorbate 80, Choline, Inositol)

"A unique physiochemical complex"

Supplied: Bottles of 12 fl. oz.
Literature available

PORTRAIT OF AN APPETITE IN RELAPSE . . .

When this supper-time still life is the picture you see in convalescence,

prescribe **TROPHITE®**

to stimulate appetite and speed recovery

Each tablet or teaspoonful (5 cc.) of 'Trophite' supplies: 25 mcg. B_{12}, 10 mg. B_1

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Rauwiloid®

The original alseroxylon fraction
of India-grown Rauwolfia
serpentina, Benth.

All the hypotensive alkaloids of Rauwolfia—not merely a single isolated substance

Free from the dross of the whole root
Gently antihypertensive
Tranquilizing
Bradycrotic
Free from undesirable side actions
Single daily dose

DOSAGE: Merely two 2 mg. tablets at bedtime. After full effect 1 tablet usually suffices. Available in bottles of 60, an average month's supply.

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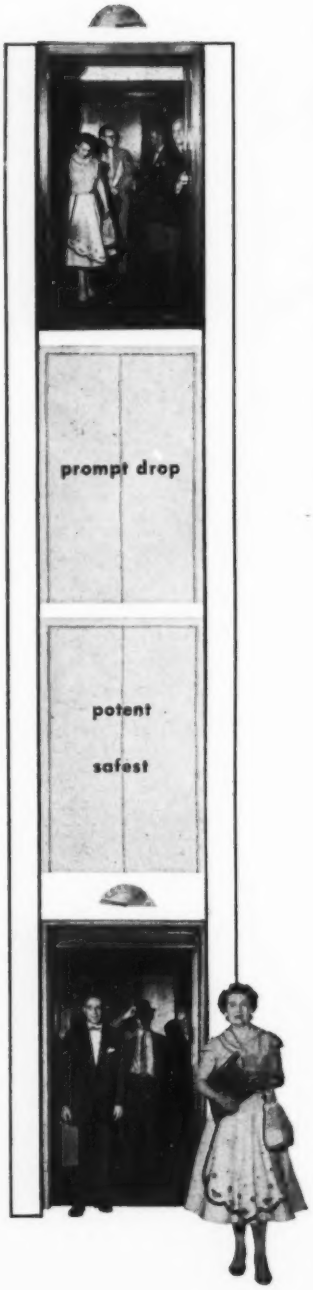

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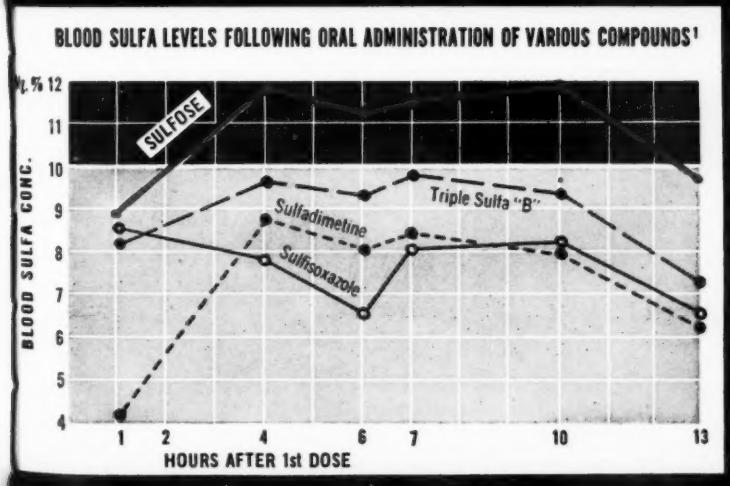

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1. Berkowitz, D.: Antibiot. & Chemo. 3:618 (June) 1953

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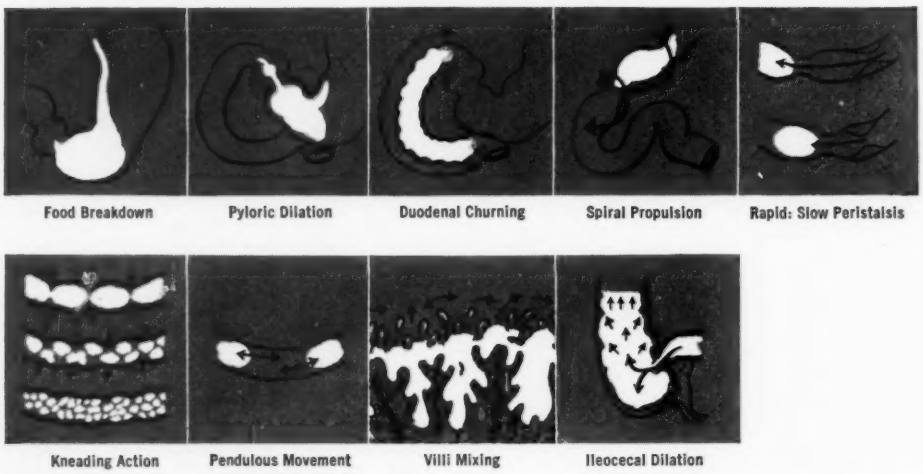

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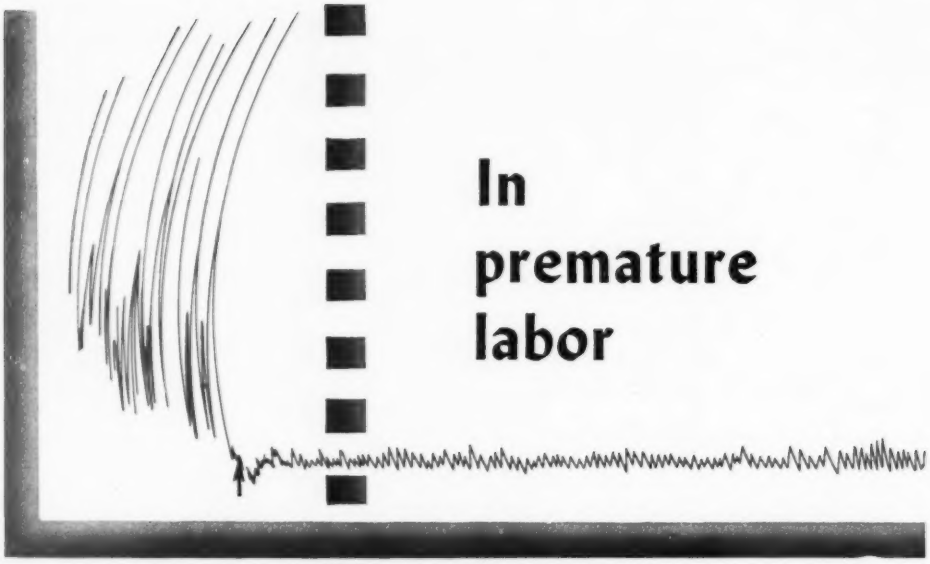

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1. Jones, Georgeanna S. and Smith, Frank: Am. J. Obstet. Gynecol., Vol. 67: No. 3, 628-633, 1954.

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Values in Medicine*

R. L. SANDERS, M.D., *Memphis, Tenn.*

SIGNIFICANT MOMENTS in life are often marked by profound emotions. This is a significant moment in my life. The Southern Medical Association was organized in 1906, the year I entered practice. I was admitted to its membership soon thereafter, and ever since it has been one of my chief interests. Now, after having been honored with its presidency during the past year, I feel that this is the climax of my career. It is a splendid moment, too, in which my heart is filled with gratefulness for your trust in elevating me to your highest office and my mind is filled with happy remembrances of our long comradeship.

Every doctor is either a philosopher by nature or he becomes one by experience, or both. When natural inclination is combined with experience, as in my own case, philosophy holds a peculiar fascination. For this occasion, therefore, I have allowed myself the pleasure of reflecting upon the essential values in medicine and the place they have held in medical progress since our association was organized.

To one who has observed the development of medicine and surgery first hand during the past 50 years, there can be no more dramatic spectacle. In 1906, medical schooling was completed in three years, and for the vast majority of doctors that was the end of professional training. The young neophyte then settled in his home town or some neighboring city and "hung out his shingle." His material equipment consisted of a table, chair and desk, a stethoscope and thermometer, a few phials of medicine, a little ether or chloroform and a handful of instruments. His lack in training and equipment, however, was compensated for by the use of his five senses and the exercise of sound judgment, ingenuity, courage, understanding and tolerance. With these basic values, embellished with fine ideals and a sincere interest in his fellow man, he perfected the art of medicine and at the same time enlarged its science. We still think of many physicians and surgeons of that period as "giants" of the profession, though there were many thousands who, in their own communities, could have been so described with equal aptness.

Early in the second decade of the century the art of medicine began to decline and the values which its masters exemplified faded from the professional consciousness. A transition took place as pursuance of cold, impersonal scientific facts became the absorbing interest. Formal training was extended to four years of college and one or two years of internship. As specialization increased, teaching was given over to specialists, each instructor being concerned only with teaching in his particular field. Laboratory procedures supplanted the use of the five senses and interest in the acquisition of individual diagnostic skill declined almost to the vanishing point. In practice, patients came to be regarded as hardly more than mechanisms. They were passed from one specialist to another, to be examined and treated by each according to his own specialized knowledge, always at considerable inconvenience and extra cost to themselves and sometimes with unfortunate consequences. Here and there a protesting voice was heard crying in the wilderness, but in general it fell upon deaf ears. The sacrifice of the art to the science of medicine was practically complete.

This period of devotion to scientific pursuits continued for 30 years or more. In reality, it was a brilliant period, in which doctors laboring in every field produced contributions surpassing those of the previous two or three centuries. By their efforts, the average span of life was lengthened many years,

*President's address, Opening Assembly, Southern Medical Association, Forty-Ninth Annual Meeting, Houston, Tex., November 14-17, 1955.

and illness was curtailed and suffering relieved to a degree previously unimagined. Their discoveries, moreover, served as the foundation of ever new developments, from which we are benefiting today and will continue to benefit. They initiated modern medicine.

Nor has the fervor of the scientific spirit diminished to the present time; rather, it has increased, and rightly so. During the past decade, however, we have come face to face with the necessity of a reappraisal of the values in medicine. The hand of events both without and within the profession has aroused us from our concentration upon science alone and startled us into the realization that there are other values which must be preserved.

One indication of this new trend of thought is to be found in the changes in our medical school curricula. A number of schools have awakened to the dangers of over-specialized teaching and the advantages of instruction in the actual care of that large majority of patients whose ills are within the realm of the general physician. They are realizing, as Dr. Harry B. Zimmermann pointed out in his presidential address before the Western Surgical Association a few years ago, that specialization should be inclusive and not exclusive; in addition to, rather than at the expense of basic knowledge and a well balanced general training. Accordingly, these schools are now providing training in general practice in teaching hospitals or through preceptorships. In this manner, the student not only gains experience in the diagnosis and treatment of disease; he also develops self-reliance and good judgment, and learns how to command the respect and confidence of patients—all indispensable in his subsequent career.

In his autobiography, Dr. Lewis J. Moorman correctly stated that "In a broad sense, the welfare of the world is within the purview of the medical school." Since the character of formal training received by the student will largely serve as a pattern throughout his professional life, it is obvious that the welfare of the world can best be served if this training includes every phase of medical practice.

Subservience to the laboratory is likewise being looked upon with disfavor today. No longer is it considered sound medical practice to subject patients to push-button technics. Laboratory studies are often unreliable and, at best, are valuable only as adjuncts to diagnosis and treatment. Even the heads of our better laboratories are calling attention to this fact. In keeping with the changing viewpoint, emphasis is currently being placed more and more where it belongs: upon a thorough history and clinical examination.

To a considerable degree, the present transition has been brought about by events in the national government, and in particular by the threat of socialized medicine. Of all the values which we are committed to preserve, our professional liberty is the one to be most cherished. Deprived of it, even our proud science would be brought to knee. The struggle to enslave medicine by socialism is still being waged under various guises and we, as guardians of the health of the nation, have a sacred charge to withstand its malicious force, whatever the cloak it wears. It has already been proved that our profession is able to solve its own problems to the best advantage of both the public and ourselves. It can always do so, provided every one of its members remains alert and continues to work without ceasing. Let none of us forget that the professional freedom of every doctor in the country is inseparable from the freedom of medicine as a whole, and that both are still at stake.

There are evidences that personal and ethical values, also, are today acquiring new emphasis. Ludwig Lewisohn expressed the opinion that physicians are almost the only class of men worthy of great respect left in our society. Such an opinion undoubtedly springs in part from the fact that physicians are presumed to be governed in their conduct by the strictest ethical code. That certain personal values are requisite to ethical conduct is being reaffirmed and insistence upon their preservation has become a watchword in professional circles. The noblest of these values and the most essential are honesty and integrity. They are our immediate jewels. If the respect of the public is to be retained, not one of us can be absolved from the exercise of integrity and honest dealing in every contact among ourselves, with our patients and with the public itself.

Aside from these qualities, the high esteem

in which physicians are held arises from the fundamental ethic of medicine, which is service devoted to the preservation of life. Each of us places his own evaluation upon medical service. To the truly ethical doctor, it has two components, the first of which may be regarded as professional awareness. This has both an individual and a general connotation.

Sound medical service depends primarily upon individual scientific fitness, which in turn depends not only upon adequate formal training, but also upon the continued pursuit of knowledge throughout one's career by study and affiliation with professional groups. The rapid pace of developments in medicine permits no surcease from learning, even for a short while. Since knowledge is nothing more than an accumulation of individual observations, however, contributions to knowledge by reports of one's own studies and experiences become an essential feature of medical service. Fortunately, it is a feature in which all can participate. It is good to see that doctors everywhere are growing more aware of these values. The current number of professional organizations, the increasing attendance at meetings and the voluminous literature on every subject are proof of this fact.

In a broader sense, professional awareness involves the recognition of one's obligation to promote the advancement of medical service in all of its tangential phases. Here, again, a new spirit is pervading our ranks. Our present outlook includes a number of endeavors of an extracurricular nature, so to speak, such as expansion of public health facilities, educational campaigns, low cost medical insurance, and group research devoted to the prevention, diagnosis and treatment of specific diseases. All of these projects are made possible through the efforts of physicians who realize that medical service has many aspects, each with its own values, and are concerned with exploring and developing the entire field for the universal welfare.

Essential as the scientific and practical aspects of medical service are, they do not completely fulfill its mission. To these must be added the second component, that transcendant quality which we call humanitarianism and wherein lies the art of medicine. Osler had this component in mind in writing that "After science in cold calculation satisfies the head, there is something wanting unless the doctor has found a fallow spot in the heart of his patient." This concept, so well understood by the doctor of 50 years ago, is being brought to the fore again today. We are rediscovering the fact that the mental and spiritual health of the individual are closely related to his physical health. The complexities of our present mode of living, with its daily stresses, have created a demand for something more than a laboratory test, a prescription or even an operation. One needs only to look into the waiting rooms of the psychiatrists to confirm this truth; they are always full. Every physician, however, can help to resolve the psychological and spiritual conflicts of his patients by understanding and sympathy. He can always be a post of stability upon which tired bodies and weary souls may lean for recovery of their whole well-being. In such a role, he fulfills completely the mission of medical service.

Just now we are hearing a great deal of discussion among doctors in every field of practice about public relations. The whole point of these discussions is that we have a duty to our patients and to the public above and beyond the limits of strictly medical care. Simply stated, public relations is but the aggregate of our individual relations in all our daily contacts. The enlarged sphere of medical service has placed us in a more conspicuous position than ever; thus, it is more necessary than ever before that our lives exemplify the humanitarian virtues as well as personal integrity and scientific fitness. With this triumvirate of values as the standard of every member of the profession, the problem of public relations would cease to exist.

One of the most far-reaching developments in medicine within recent years, and striking evidence of the present trend of thought among us, has been the restoration of general practice to the dignity of its former position. It is a response to the wish of large numbers of people for a general physician whom they can consult for all their ills and upon whom they can rely for reference to a competent specialist should the need arise. It opens the way for a broad-scale re-establishment of a relationship in which the doctor is not only professional consultant, but personal friend

and counsellor. With the growth in our population, a more health-conscious public and an increasing longevity, the field of the general physician is constantly expanding. More and more, therefore, he will be able to exercise all those values of mind and spirit which add the crowning glory to medical service.

I like to think that the present awakening in medicine is a part of the spiritual awakening which has become everywhere apparent within recent years. No longer is religion a matter of indifference to the vast majority of people; it is a powerful guiding force in their daily lives. Certainly, it should be the power which guides those who minister to diseased bodies and distressed souls. In contemplating all the beneficent changes now taking place in our profession, one must conclude that a renewed religious consciousness is their basic inspiration, their underlying value.

It has been a priceless experience to have observed the stages of growth of medicine during the past half century: first, the dominance of art, then the dominance of science, and today, I rejoice to say, the transition to full maturity in which science and art will be united. The Southern Medical Association has always upheld the values which have made this growth to maturity possible. It will continue to uphold them until the transition is complete and thereafter, that medical service may be maintained unceasingly at its highest scientific and artistic level.

Stephen Paget called medicine the "divine vocation." Truly, no other profession can offer so many satisfactions. When service devoted to the preservation of life is motivated by a spirit of true dedication, it blesses him that gives as well as him that receives. As the ethical and humanitarian values which illumined medical practice 50 years ago become integrated with modern science in all its splendor, it may be repeated, but with far more inclusive meaning, that medicine is indeed a divine vocation.

The Radiologist's Responsibility in Making the Diagnosis of Pancreatitis*

KIRK R. DEIBERT, M.D., *Florence, Ala.*

The differential diagnosis of pancreatitis from other abdominal diseases is often a difficult one. The author describes the details of his x-ray examination to aid in diagnosis.

THE RADIOLOGIST is frequently requested by the clinician to examine a patient with upper abdominal pain. The preliminary clinical differential diagnosis revolves about the following: (1) Myocardial infarction; (2) renal colic; (3) appendicitis; (4) ileus or peritonitis; (5) gallbladder or extra-hepatic biliary tract disease; (6) peptic ulcer, either gastric or duodenal; and (7) pancreatitis.

Approximately six years ago I became interested in the anatomy and pathology of the pancreas. This interest started with a request made by the surgical service upon the x-ray department. They wanted some help from a radiologic standpoint in establishing the diagnosis of pancreatic disease. As the correlative study took form it grew into a differential radiographic diagnostic procedure. It became apparent that a routine gastrointestinal roentgenologic examination could on many occasions serve as a diagnostic aid to the surgeon. By keeping in mind the normal manifestations of anatomy and physiology as identified in the roentgenologic examination of the upper gastrointestinal tract, slight de-

*Read before the Section on Radiology, Southern Medical Association, Forty-Eighth Annual Meeting, St. Louis, Mo., November 8-11, 1954.

viations from normal could be detected. This requires an intimate exchange of information between the surgeon and radiologist. It means further that the radiologist be present at the operating or necropsy table to increase his knowledge and acumen.

X-ray Diagnosis in Upper Abdominal Disease

A perusal of the standard textbooks on radiology and the Cumulative Index failed to reveal any significant information on this subject. Much has been written about the x-ray changes of the descending duodenum accompanying malignancy of the head of the pancreas and periampullary area. Most clinicians are familiar with the radiographic significance of the so-called, reversed "3" sign of the second duodenum. Pancreatic cysts are usually easily demonstrated. A calcareous outline of the pancreas implies chronic pancreatitis. It is not with these latter conditions that I am concerned.

My study is concerned chiefly with the differential points in establishing the diagnosis of peptic ulcer, biliary disease or pancreatitis. Some of the important features of the differential diagnosis will be given.

1. The clinician will determine the presence of *myocardial disease* by history and physical examination. He has recourse to the electrocardiogram or a routine chest roentgenogram. This latter is apt to reveal a prominence of the aorta and left ventricle. If there is noted an unusual blunting of the left cardiac border just above the apical junction with the diaphragm, an infarct can be diagnosed. The abnormal pulsation of the heart can be identified by fluoroscopy. Early congestive changes may also be present. The plain film of the abdomen may or may not be of help; occasionally a minimal gaseous bowel distention may be observed.

FIG. 1

There is marked bulbar dilation; the second part of the duodenum is narrowed, irritable and irregular. There is a plaque of pleural calcification in the right lung base. The retroduodenal calcification is a large right renal calculus, verified by pyelogram, and at operation. The inner sweep of the second duodenum is broadened due to pancreatic enlargement; two calculi are lodged in the pancreas.

2. *Renal colic* as a rule presents a fairly typical clinical trend of events. Following the urine analysis, a plain film of the abdomen usually reveals a calcareous zone along the course of the urinary tract. A pattern of ileus in the small bowel is apt to be noted. If needed a pyelogram can be done. This will usually demonstrate the exact site of the opaque calculus or perhaps a nonopaque calculus (Fig. 1).

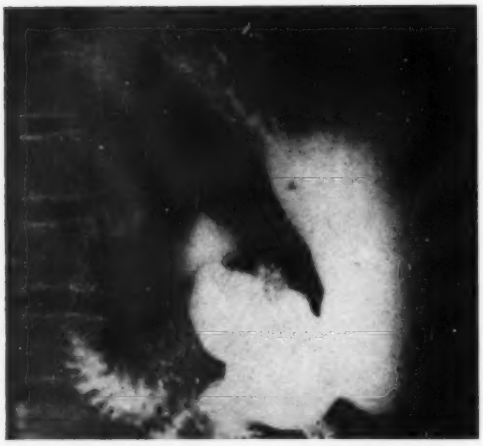
3. A plain film of the abdomen may be helpful at times in the diagnosis of *appendicitis*. If a fecolith is demonstrated prior to perforation, immediate operation should be done. Occasionally a slight stasis or ileus pattern may be present in the right abdomen or a soft tissue mass may be noted.

4. *Peritonitis* gives a fairly typical distribution of air in the small bowel with distention. The psoas lines or the lateral abdominal parietes may be blunted, partially obliterated or deviated. Following serial radiographic study of the abdomen a localized displacement of the loops of the small bowel may be recognized. This would indicate an intra-abdominal abscess. With progression of the peritonitis the spacing between the individual bowel loops may be increased. This indicates intra-peritoneal fluid and further progress of the obstructive feature of peritonitis.

5. Positive *biliary calculi* are identifiable on a routine 'scout film' of the abdomen. About 10 per cent of biliary calculi cast a dense calcific shadow. They can usually be recognized by their position. However, a right lateral, detail 'spot film' will distinguish a renal from a biliary opacity. A cholecystogram will detect the presence of negative radiolucent calculi. The accuracy of this examination is about 95 per cent correct (Fig. 2).

6. *Peptic ulceration* can be determined readily by an upper gastrointestinal study.

FIG. 2



Pressure upon the duodenum by an enlarged and diseased gallbladder, shown to be non-functioning by cholecystography, and verified at operation.

Everyone is familiar with the niche of gastric or duodenal ulcer. Most frequently this is not found but the deformity is revealed following scar formation at the ulcer. At times the exact location of the ulceration is not determined. This follows the so-called 'straddle-isthmic' ulcer where the distortion is marked and the distal gastric landmarks are obscured. This renders difficult the exact localization of the deformity. The ulceration may be duodenal or prepyloric at the initial examination, a second examination is occasionally needed to settle this point (Fig. 3). Even without the gross presence of subphrenic air following perforation of a duodenal ulcer, the preliminary plain film of the abdomen can be helpful. A globular distribution of air, not conforming to duodenal outline, may be identified at the junction of the right renal and psoas lines, indicative of a low grade perforation. Lateral displacement of the gastric 'air bubble' associated with a hazy, 'droplet-like' distribution of air adjacent to the left paravertebral gutter is indicative of perforation of a posterior gastric ulcer into the lesser omental sac.

Radiologic Studies

This study involves the performance of a gastrointestinal series as the source for a radiologic clinical impression. Approximately 200 cases have been reviewed and analyzed. This procedure assumes an adequate survey of the component parts of the thorax, including a careful scrutiny of the aortic and cardiac profile. By this method cardiac infarcts may be determined. Every patient is given a bolus of thick barium paste to swallow to better appreciate alterations of the esophageal mucosa. The filled esophagus reveals to better advantage reflected posterior pulsation of the cardiac chambers upon the opaque column. Diaphragmatic excursion is noted as well as pleuropulmonary densities. Alteration in the basal angles of the lung may accompany either biliary or pancreatic inflammations. Other causes of such changes as subphrenic or subhepatic abscess, or a splenic infarct are not within the province of this study. The mucosal profiles of the stomach and duodenum are studied. This is accomplished in the routine manner resorting to the pressure 'spot film' device when indicated.

Concerning abnormalities of the pancreas an evaluation of the patient's build for the gastric-duodenal-spinal relationships must be made. This notation is recorded for each patient to include current weight and general habitus. During the course of this study a record sheet was used for types of body build and for weights. This included those who were considered normal and abnormal so that three measurements could be obtained. On the postero-anterior projection of the stomach

FIG. 3

Ulcer crater of inferior portion of first duodenum. Marked periluminal pancreatic edema and barium stasis are present in the second duodenum.

one measurement (M-3) is obtained from the mid-spinous line to the inner medial aspect of the second duodenum. The other two measurements are obtained from the right lateral projection of the stomach. One measurement (M-1) is obtained by measuring the distance from the ventral surface of the second lumbar vertebra to the junction point of the prepyloric stomach and posterior duodenal bulb base. The second measurement (M-2) is obtained similarly except that the line is extended to the angulus. It was found that in the hyposthenic build the descending duodenum is apt to approach or overlie the spine on the lateral projection. In contrast to this, for the sthenic and hypersthenic build, the descending limb lies at varying distances ventrad to the spine. For the postero-anterior projection the duodenum usually is lodged further lateral to the spine for those of sthenic build than for the asthenic group. The exception to this is in case of the long, atonic, ptotic stomach.

The following measurement ranges were obtained: (Fig. 4)

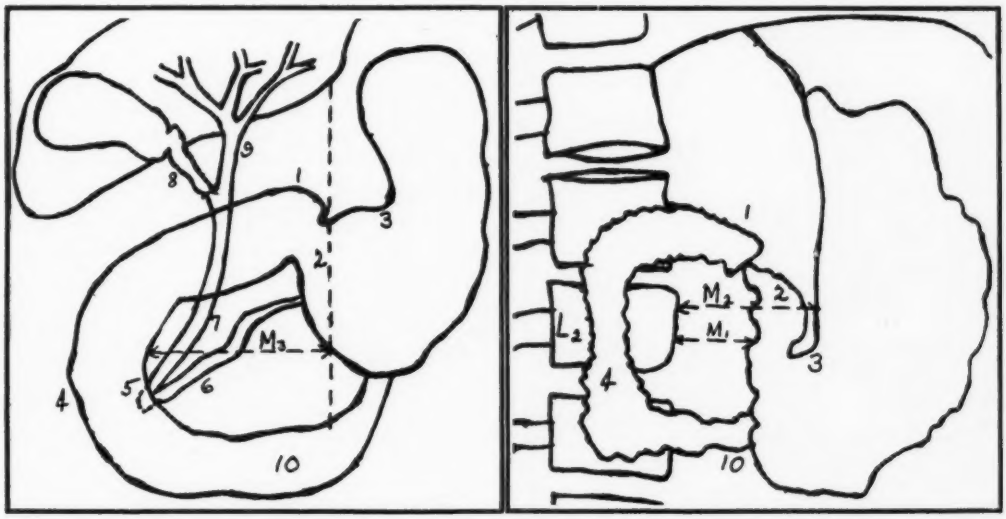
	M-1	M-2	M-3
Sthenic	6.5-8.5 cm.	8-16 cm.	2.5-6.5 cm.
Asthenic	3-5 cm.	7-10 cm.	3.5-4.5 cm.
Average	6.0 cm.	8.0 cm.	4.5 cm.

The examiner at the fluoroscopic screen should be alert to the possible existence of pancreatitis by the replies he obtains in answer to his routine queries. This is coupled with the appearance of the opacified stomach and duodenum. Help may be gotten by eliciting local tenderness to palpation during the examination. The following items are important points for establishing the diagnosis of pancreatis.

1. For the preliminary 'scout film' of the abdomen, patchy or segmental relatively dilated loops of upper small bowel should suggest possible pancreatic ileus. An added finding may be a considerable amount of air in the transverse colon which may be depressed in the mid zone. A hazy appearance in the upper mid-abdomen with a lateral tilt to the gastric air pocket suggests pancreatic edema and lesser omental bursal fluid to be present.

2. Following a barium contrast study the appearance of a serrated mucosal profile for the lesser curvature of the transverse gastric strait is to be noted. The channel may be thinned and tapered as it approaches the isthmus. Depending on the anatomic location and extent of the pathologic change in the pancreas there may be an arcuate elevated zone at the distal prepyloric greater curvative

FIG. 4



A B

Measurements for gastric-duodenal spinal relationships. (A) Anterior projection: 1. Duodenal bulb, 2. prepyloric stomach, 3. gastric angulus, 4. descending duodenum, 5. duodenal ampulla. (B) Lateral projection: 6. Pancreatic duct, 7. common duct, 8. cystic duct, 9. hepatic duct, 10. transverse duodenum.

of the stomach. There may be concave thinning at the angulus extending into the lesser curvature zone of the pars media (Fig. 5).

3. The duodenal loop may be deviated laterally and/or dorsally. The appreciation of this duodenal sweep has a direct relationship to the component part of the spinal measurements given above.

4. There may be a general anterior deviation of the stomach while the duodenal bulb is elevated superiorly.

5. Disturbed and altered barium motility and mobility may be identified both for the stomach and duodenum.

6. The mucosal markings of the entire descending duodenum need close scrutiny. Flattening of the inner aspect of the valvulae conniventes or coarsening and edema of the mucosal folds indicate periluminal pancreatic inflammatory reaction.

7. The edema may be particularly manifested at the periampullary zone, or an exaggerated lateral convex bulge may be apparent.

8. Duodenal stasis and ileus occurs frequently.

FIG. 5

Typical gastroduodenal changes accompanying pancreatitis, verified at autopsy. A subphrenic abscess also was present.

9. The ligament of Treitz may be depressed.

10. There may be an undulated appearance of the inferior margin of the stomach distally and also of the inferior margin of the first and third portions of the duodenum.

11. Since biliary disease is a frequent precursor of pancreatitis search should be made for an abnormal cholecystogram or for calculi.

12. Pancreatic calculi are diagnostic in themselves.

13. Colonic stasis may be evident, or if opacified extrinsic pressure will be noted upon the mid transverse colon with irritability.

14. Ileus of the small bowel and pattern of a segmental stasis is to be noted on the interval radiographic bowel study.

15. The individual spacing of the small bowel loops may be increased incident to exudation of intraperitoneal fluids.

16. The space between the transverse stomach, duodenum and colon is apt to be widened due to pancreatic edema. This may be enhanced by inflammatory reaction in the interposed omentum.

17. Basal pulmonary or pleura reaction is to be noted if present.

18. Occasionally a localized zone of altered mucosa in the mid-portion of the second duodenum may be identified. It is difficult to distinguish this from a primary ulceration. However, pancreatitis alone can be a cause of secondary ulceration.

There are other causes for the changes described above either considered partially or totally.

Inflammatory change in the region of the right renal bed can produce many of these alterations. However, bulbar or gastric displacement will not be observed unless a perirenal abscess causes deviation of the descending duodenal limb. The presence of opaque renal or ureteral calculi will establish the correct impression (Fig. 1). Scarring due to ulcer of the second portion of the duodenum is a common cause for a bulbous, boggy outline of the duodenal cap. It frequently is associated with periluminal inflammatory reaction. This is a common cause for edema and inflammatory change in the head and neck zone of the pancreas (Fig. 2). Pen-

TABLE 1

CLASSIFICATION OF ROENTGENOLOGIC FINDINGS

	Cases	*Verified**
1. Pancreatitis, chronic, calcific	17	a, b, c
2. Pancreatitis, acute, edematous	20	a
3. Gallbladder disease, with or without stone, hydrops	13	b
4 Ulcer, prepyloric	3	a, b, c
Ulcer, bulbar	13	a, b, c
Ulcer, second duodenum	5	a, b, c
5. Combined inflammatory change of gallbladder, pancreas and/or duodenum	3	a
6. Carcinoma of pancreas, head or ampullary	14	b, c
7. Carcinoma of gallbladder	1	b, c
8. Carcinoma of prepyloric stomach or antrum	2	b, c
9. Carcinoma, inflammatory type, hepatic flexure	1	b
10. Duodenal obstruction, partial, tumor, mesenteric	4	b
11. Duodenitis	4	a
12. Renal disease	2	b
13. Pancreatic cyst	5	b
14. Altered duodenum, miscellaneous, lymph nodes	4	b, c
15. Interpretation, abnormal, proven negative	6	b
Causes of Misinterpretation		
Carcinoma of pancreas and ampulla	4	
Carcinoma of gallbladder	1	
Pseudo-cyst of pancreas	1	
Gallbladder disease	4	

* a.—Verification by clinical laboratory study. b.—Verification by operation. c.—Verification by autopsy.

etration of a posterior gastric or duodenal ulcer can cause marked secondary inflammatory reaction in the pancreas.

A close observation of the appearance of the mucosal markings in the proximal part of the second portion of the duodenum may lead to the diagnosis of biliary disease. Localized irritability with evidence of extrinsic pressure laterally will suggest cholecystitis. Distortion from adhesions may be noted but not a constant defect which could be attributed to an ulcer deformity. Secondary duodenal stasis with a dilated bulb is likely to be present. A distended gallbladder will cause a concave impression upon the upper lateral duodenal profile. At times, with radiographs having a sharp contrast, the dilated primary outline of the gallbladder is to be observed.

On occasion an indefinite mass is palpable clinically in the right upper abdomen. Preliminary scout films should be obtained initially including a lateral recumbent projection prior to any contrast study. These procedures may localize a collection of air to indicate the presence of a subphrenic or subhepatic abscess. A barium enema is also helpful to determine displacements of abdominal viscera. It may indicate the origin of the mass, namely a diverticulum of a flexure or a typhlitis due to an abnormal location of the appendix.

Summary

A radiologic study has been made in an attempt to distinguish between the causes of upper abdominal pain. The clinical impression initially revolves about the three most frequent causes of pain: Namely, peptic ulcer, biliary disease and pancreatitis. Quite frequently the clinical entity can be identified by the appearance of the opacified stomach and duodenum following an upper gastrointestinal barium study. The localized or generalized altered barium profile of the stomach and duodenum in relationship to the spine has been presented in differentiating these three clinical entities. At times several other clinical entities need to be excluded in the total differential diagnosis. Certain radiographic examinations are offered and the salient radiologic features of the suspected disease is given.

Acknowledgment is made for the initial help provided by Dr. John Beveridge, Nashville, Tenn.

Annular Pancreas*

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This congenital anomaly is a rare one. Nevertheless, if one thinks of it the diagnosis may be suspected; the x-ray findings seem pathognomonic.

CONGENITAL ANNULAR PANCREAS as a cause of obstruction of the duodenum is a rare anomaly. However, five cases of annular pancreas have been seen at the John Gaston Hospital within a period of three years. This experience has indicated that the lesion can oftentimes be diagnosed preoperatively with considerable accuracy. The purpose of this paper is to describe and illustrate the radiologic findings, which are of paramount importance in differential diagnosis.

With the exception of the cases reported from this hospital, only 37 surgically treated cases have been found in the literature. Annular pancreas has been described in an infant two days of age and in a patient 74 years of age. Including the cases in this report, 23 cases have been in adults and 19 in children. All five of the cases we have observed have been in children—four in the neonatal period, and one at twenty months of age. This is particularly significant, as the cases were seen in a general hospital in which the majority of the patients are adults.

The anomaly consists of a thin band of pancreatic tissue arising from the head of the pancreas and completely encircling the descending portion of the duodenum. Embryologically the ring of pancreas probably arises from the ventral anlage. The encircling ring produces varying degrees of duodenal obstruction. Cases have been reported in which there was no obstruction and the anomaly was an incidental finding of no clinical significance, discovered only at autopsy. Other cases have been reported in which there was a complete underlying atresia of the duodenum. Depending upon the degree of obstruction, there is dilatation and thickening of the wall of the duodenum proximal to the pancreatic ring.

The symptoms caused by an annular pancreas depend upon the severity of the obstruction. In all five of the cases we have seen the obstruction was rather marked, but in no case was obstruction complete. Therefore, symptoms began early in life and were just what one would expect from any partial obstruction high in the gastrointestinal tract. Vomiting is the cardinal symptom and is projectile in type in some patients. The vomitus usually does not contain bile. Epigastric pain may be associated with the vomiting. In infants, visible gastric peristaltic waves may be noted in the upper abdomen, but no pyloric mass can be palpated.

The radiologic findings are essentially dilatation of the proximal portion of the duodenum and an abrupt, smooth, concentric narrowing of the descending duodenum with rather marked but incomplete obstruction.

Case Reports

Case 1. G. D., a white female, was born at the John Gaston Hospital on January 1, 1951, a full term normal birth.

No abnormality was noted until the third day of life, when the child began vomiting after each breast feeding. This persisted in spite of treatment with atropine and phenobarbital. Vomiting gradually became more severe. Occasionally, visible peristaltic waves were noted in the left upper quadrant, but no pyloric mass could be felt. A gastrointestinal study was requested on the eighteenth day of life. This study revealed a normal esophagus and stomach. The duodenal cap was dilated to a rather marked degree and there was an abrupt, smooth, concentric narrowing of the duodenum in its descending portion. The stomach emptied rather slowly due to the obstruction, and at four hours most of the opaque medium remained in the stomach (Fig. 1). An examination of the colon by barium enema was immediately done, and this showed incomplete rotation of the colon with the cecum in a subhepatic position. The impression at that time was incomplete rotation of the colon with an obstructing band across the duodenum.

Laparotomy, two days later, revealed the incomplete

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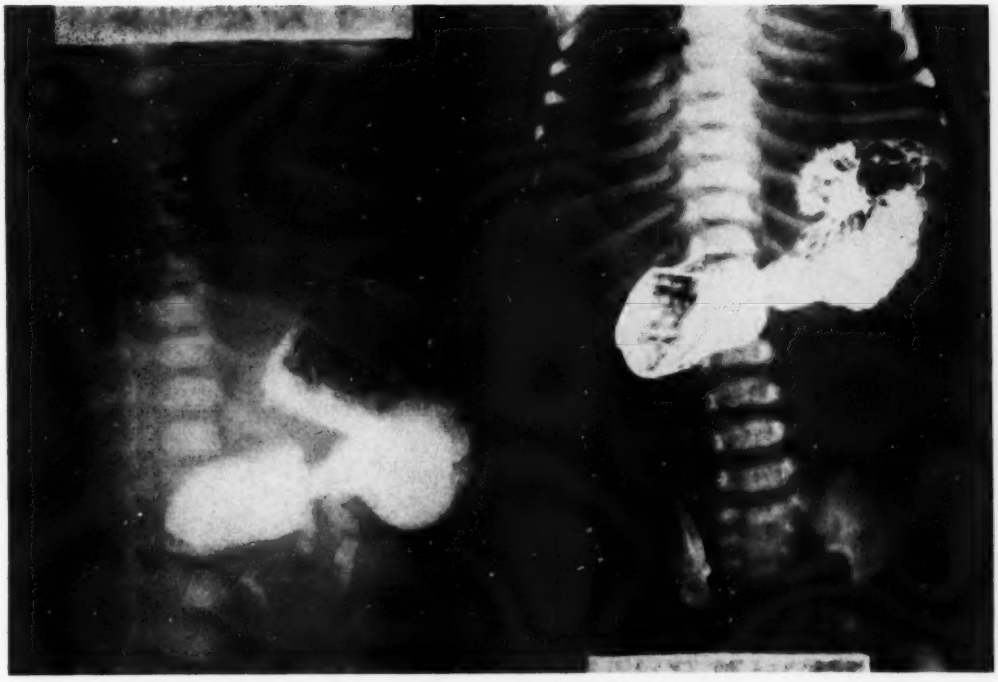
FIG. 1, CASE 1



P-A and oblique views showing marked dilatation of the duodenal cap.

rotation of the colon with the cecum high in the right upper quadrant. The cecum was adherent by a strong, short band to the peritoneum overlying the right kidney in a manner so as to constrict the descending portion of the duodenum. A band from the colon to the lower edge of the liver also compressed the second portion of the duodenum. The congenital bands were divided, after which it was noted that there was a complete ring of pancreatic tissue surrounding the descending portion of the duodenum. It was the surgeon's opinion at the time of operation that the annular pancreas was not causing much obstruction. A duodenojejunostomy was thought to be indicated but could not be done because of the poor condition of the patient.

Following operation, the patient continued to vomit all feedings, and on January 31, 1951, a second laparotomy was done, at which time the duodenojejunostomy was accomplished. The patient developed pneumonia and died two days after operation. Autopsy confirmed the diagnoses of interstitial pneumonia, annular pancreas, and incomplete rotation of the colon.

Case 2. L. E. P., a two week old, colored male, was admitted to the John Gaston Hospital on June 20, 1951. Birth had been uneventful, and the baby weighed 7 lbs., 13 oz. at birth.

The child began vomiting at five days of age. This occurred at least twice a day, often a few minutes after feeding. The vomitus had been quite copious and white in color, never bile stained. On physical examination there was mild dehydration. However, no palpable pyloric mass was demonstrated, and no peristaltic waves were seen.

The patient was referred to the Department of Radiology for gastrointestinal examination. This demonstrated a normal esophagus and stomach. There was rather marked dilatation of the proximal portion of the duodenum, and a smooth, concentric, abrupt narrowing of the upper part of the descending portion of the duodenum. The stomach emptied quite slowly due to the partial obstruction (Fig. 2).

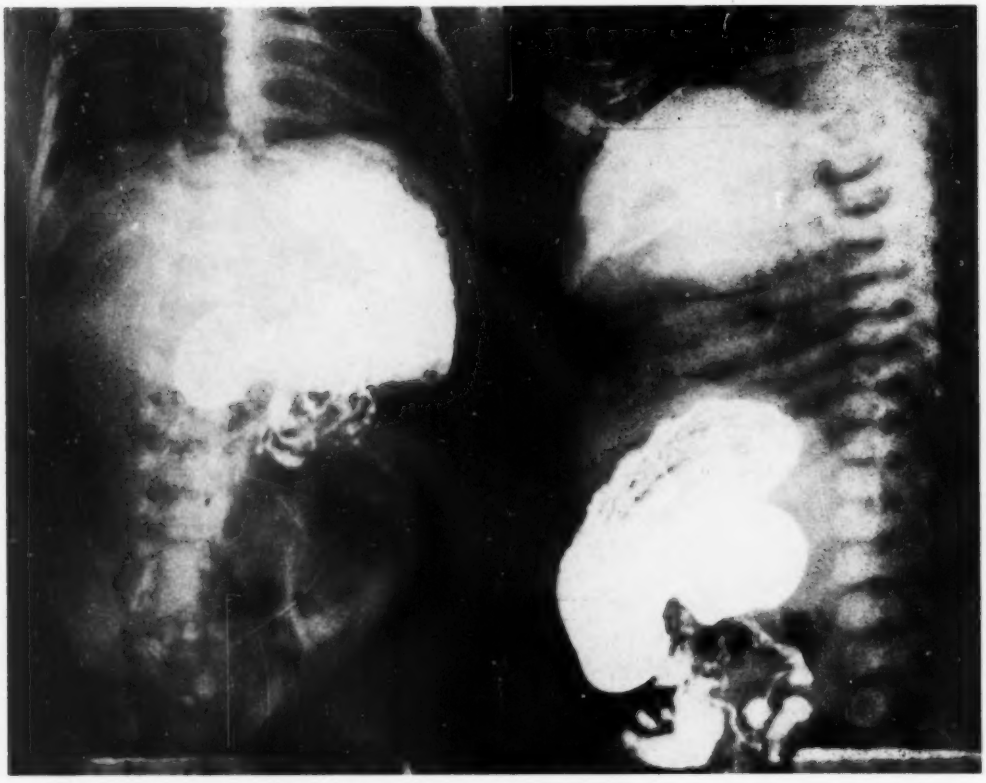
A laparotomy was done on July 3, 1951, with a preoperative diagnosis of partial obstruction of the descending portion of the duodenum, cause undetermined. At operation the obstruction was found to be due to an annular band of pancreatic tissue completely surrounding the duodenum. A posterior gastrojejunostomy was done. The patient had an uneventful recovery and is still living and well.

Case 3. E. B., Jr., a 20 month old, colored male, was admitted to the John Gaston Hospital on May 13, 1952, with a complaint of intermittent vomiting since three days of age.

Vomiting was projectile in type, and the vomitus was often copious in quantity. On physical examination there was a moderate degree of malnutrition and mild dehydration. No pyloric mass was felt.

The patient was referred for a gastrointestinal

FIG. 2, CASE 2



Oblique and lateral views. The lateral film shows abrupt concentric narrowing of the duodenum distal to the cap.

study on May 16, 1952, with a clinical diagnosis of congenital anomaly of the gastrointestinal tract, pylorospasm, or hypertrophic pyloric stenosis. X-ray examination showed slight dilatation of the stomach with moderate hyperperistalsis. There was marked dilatation of the duodenal cap and immediate post-bulbar region of the duodenum. There was a smooth, concentric constriction of the duodenum in its upper descending portion. At four hours only about 15 per cent of the barium meal had passed through the obstruction (Fig. 3). An incidental finding was a steel ball, 1 cm. in diameter, in the dilated duodenal cap. (The history did not disclose when this had been swallowed.)

Because of the location and appearance of the partially obstructing lesion, a diagnosis of congenital annular pancreas was made. Laparotomy was done three days later, and the annular pancreas, completely encircling the second portion of the duodenum, was found. Proximal to this, the duodenum was dilated to about five times its normal size, and the duodenal wall was considerably thicker than normal. A duodenojejunostomy was done. Recovery was uneventful.

Case 4. B. B. D., a one week old colored male, was admitted to the John Gaston Hospital on September 1, 1952. The baby was full term, and the birth had been uneventful. The child was brought to the hospital because of failure to nurse properly.

The history was most inadequate, but apparently vomiting had begun the day prior to admission to the hospital. On physical examination the child was extremely dehydrated. No pyloric mass was felt, but peristaltic waves were seen in the left upper quadrant.

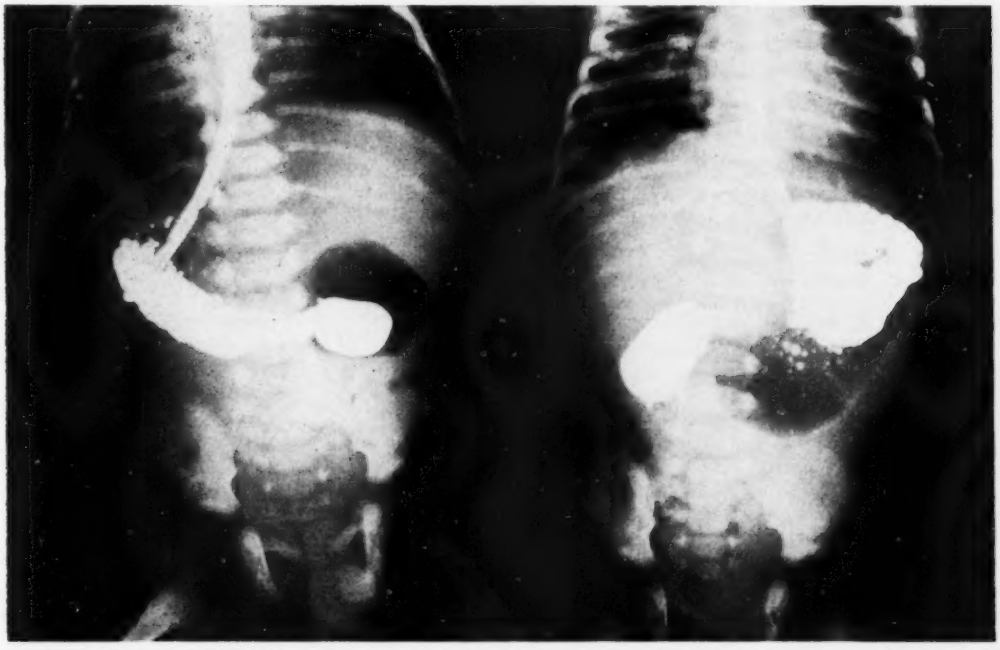
X-ray examination showed a normal esophagus. The stomach was slightly dilated and showed moderate hyperperistalsis. The proximal portion of the duodenum was markedly dilated, and in a period of one hour no contrast medium had passed through the obstruction. A small amount of gas was seen in the small intestine and colon (Fig. 4). The impression was partial duodenal obstruction due to congenital annular pancreas.

At operation the following day a 0.5 cm. band of pancreatic tissue was found to completely encircle the descending duodenum, producing almost complete obstruction. A duodenojejunostomy was performed. Following operation the child developed pneumonitis and patchy atelectasis, became cyanotic, and died on the third postoperative day. Permission for autopsy was refused, but it was believed that the death was due to aspiration pneumonia.

FIG. 3, CASE 3

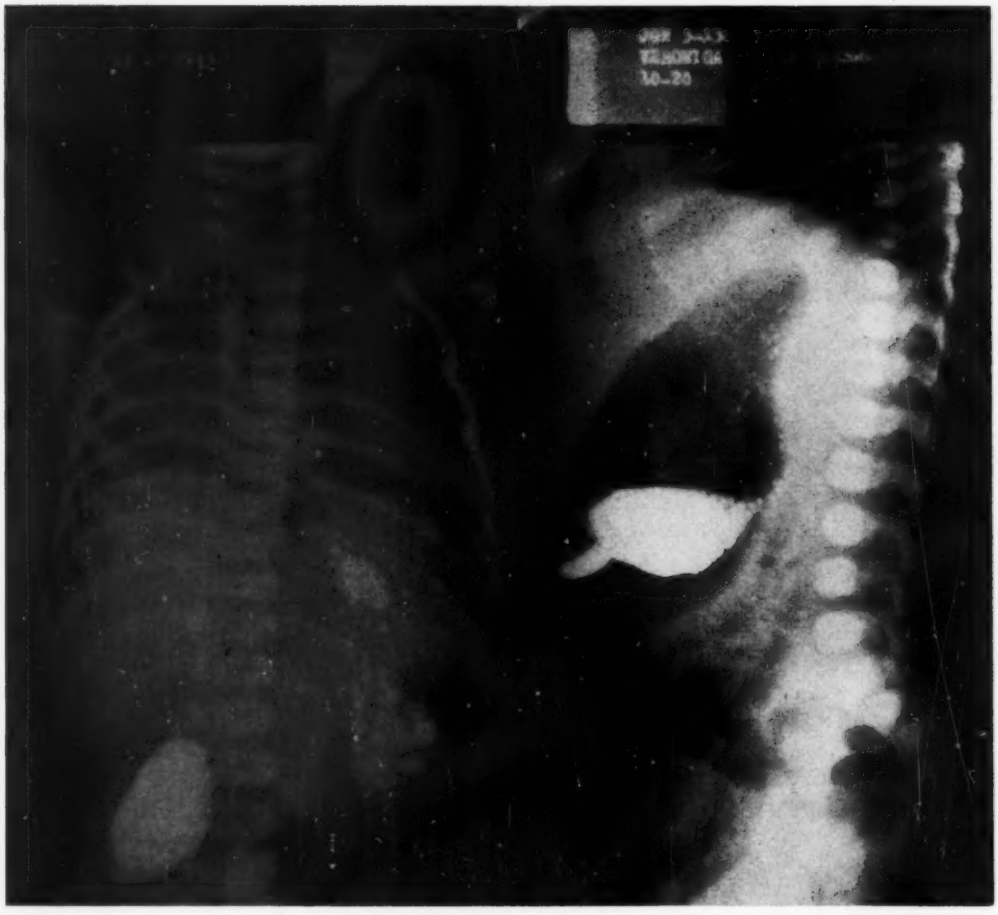
Immediate P-A film, and four hour interval film which shows marked delay in gastric emptying. The duodenal cap is markedly dilated.

FIG. 4, CASE 4



P-A and A-P views. Small bubbles of gas are seen in the intestinal tract distal to the duodenal obstruction, proving it to be incomplete.

FIG. 5, CASE 5



The lateral view shows the stomach to be filled with air. The duodenal cap filled with iodized oil is seen through the air filled stomach, and the smooth concentric narrowing of the duodenum distal to the cap demonstrated.

Case 5. V. L. S., a colored female, two weeks of age, was admitted to the John Gaston Hospital on October 19, 1953. The patient had vomited after each feeding since the third day of life.

Vomiting occurred about 30 minutes after feeding, was not projectile in type, and the vomitus did not contain bile. On physical examination marked dehydration was noted.

A gastrointestinal study was requested the day after admission. This examination showed a normal esophagus and stomach. The duodenal cap was rather markedly dilated, and there was marked but incomplete obstruction in the descending portion of the duodenum due to an abrupt concentric constriction (Fig. 5). A diagnosis of annular pancreas was made.

At operation a complete circle of pancreatic tissue was found to constrict the second portion of the duodenum. A duodenojejunostomy was done. Postoperative recovery was uneventful and the baby has remained well since.

Discussion

In reporting a case of congenital annular pancreas in 1950, Haden[1] made two interesting statements,—firstly, that the "preoperative diagnosis is almost unheard of," and secondly, that "once an example has been encountered and impressed upon the mind, any subsequent case is pretty obvious." The first patient we encountered had an associated incomplete rotation of the colon with compressing bands, and although we had had no experience with congenital annular pancreas at that time, it is doubtful that the diagnosis

of the second congenital anomaly would have been justified.

The preoperative diagnosis on the second patient was partial obstruction of the duodenum, cause undetermined. The fact that a diagnosis of annular pancreas was not made on that patient can only be attributed to lack of experience. Since then a correct diagnosis has been made on all the patients with annular pancreas encountered. Furthermore, a diagnosis of annular pancreas has not been made on a patient who failed to have the anomaly. The roentgenologic findings in all five of the cases have been remarkably similar. The stomach has been normal except for varying degrees of hyperperistalsis. The duodenal cap fills without delay, and the very marked dilatation of the duodenal cap is one of the outstanding features of the anomaly. Another observation is that one cannot distinguish between the duodenal cap and the immediate post-bulbar region of the duodenum due to the marked dilatation. The duodenum then narrows in an extremely abrupt concentric fashion, and this has invariably been in the upper descending portion. In none of the patients that we have observed has the obstruction been complete.

The differential diagnosis in infants and young children with clinical symptoms and signs of an obstruction high in the gastrointestinal tract must include pylorospasm, hypertrophic pyloric stenosis, congenital atresia, and incomplete rotation of the colon with congenital obstructing bands. In pylorospasm and hypertrophic pyloric stenosis the location of the obstruction is obviously in the distal end of the stomach, and on x-ray examination annular pancreas would not be considered. If a pyloric mass can be felt, an x-ray examination is not necessary to diagnose hypertrophic pyloric stenosis. Congenital atresia can occur anywhere in the gastrointestinal tract, but we have seen only one patient with congenital atresia in precisely the same location as annular pancreas. Although annular pancreas may be associated with an underlying atresia, if the obstruction is complete it is probably safer to make a diagnosis of atresia only. In the case of congenital bands producing obstruction, the site of the obstruction is usually in the third portion of the duodenum, and incomplete or malrotation of the colon is present.

The differential diagnosis in adults having annular pancreas is obviously more difficult. Obstruction of the descending duodenum could be due to carcinoma, inflammatory lesions, post-bulbar ulcer, and adhesions. However, it would be unusual for any of these lesions to present as abrupt, smooth, and concentric a defect as that seen in annular pancreas. Furthermore, the clinical history and physical examination would be most important in differential diagnosis. Such findings as jaundice or epigastric mass would obviously be against the diagnosis of annular pancreas.

The diagnosis of annular pancreas is easiest in patients such as we have encountered, that is, in very young children in whom the lesion causes marked but incomplete obstruction. The diagnosis becomes more difficult when the lesion causes little or no obstruction, and it is much more difficult if there is an underlying complete atresia.

Hope and Gibbons[2] have stressed the importance of making the diagnosis of annular pancreas by x-ray using no contrast media. Gaseous distention of the duodenal cap with small bubbles of gas distal to the cap (the so-called "double-bubble" sign) certainly is a characteristic appearance. Gas can be used as the contrast medium as well as an opaque substance. However, the cases that we have encountered have not had a complete obstruction clinically, and the differential diagnosis included such lesions as congenital bands, hypertrophic pyloric stenosis, and pylorospasm. We have seen no contraindication to the use of opaque media, and since the divisions of surgery and pediatrics have not objected, we have preferred to use an opaque medium. In infants it is probably preferable to use an iodized oil such as Lipiodol or Iodochloral because of the risk of regurgitation and aspiration. Six to 8 cc. is all that is required for a beautiful demonstration of the lesion.

The surgical treatment of choice is probably a duodenojejunostomy. Certainly one should not attempt to relieve the obstruction by cutting across the encircling ring of pancreas. Division of the ring may result in pancreatitis or a pancreatic fistula. Also, division

of the ring usually will not relieve the situation since obstruction recurs rather promptly.

Summary

(1) Five cases of congenital annular pancreas have been presented.

(2) Roentgenologic observations are of paramount importance in differential diagnosis and include marked dilatation of the proximal portion of the duodenum with an abrupt, smooth, concentric narrowing in the descending portion of the duodenum.

(3) Duodenojejunostomy is the treatment of choice.

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Discussion (Abstract)

Dr. William B. Seaman, St. Louis, Mo. I would like to thank both Dr. Deibert and Dr. Carroll for their thought-provoking papers, and wish to express my appreciation for the opportunity of discussing these papers.

Dr. Deibert's paper covers a wide variety of topics and in the short time allotted it would be difficult for me to discuss all of the details of his paper. I just want to mention a few of the things that occurred to me.

I would like to re-emphasize his plea for close cooperation between the radiologist and the clinician. It is certainly true that if we know all of the clinical details and work closely with the clinician we can certainly do a better job, especially in the diagnosis of the acute abdomen.

There are a few things that he mentioned in his list of differential diagnoses that are not good roentgen diagnoses. I feel, that in myocardial disease and appendicitis, the radiographic portion of the diagnosis is of relatively little importance.

The region of the pancreas is certainly a radiographic blank spot in the upper abdomen; and we try to do our best by paying careful attention to surrounding structures such as stomach and duodenum.

This business of measurements of the retrogastric space is a very difficult thing to evaluate. I am sure we are all aware of the tremendous variation in the distribution and amount of retroperitoneal fat. Engel and Lysholm about 20 years ago introduced gastropneumography and attempted to measure the distance between the posterior wall of the stomach and the anterior portion of the vertebrae. They concluded that the normal width was equivalent to the width of the vertebral body. This has subsequently been found not to hold up very well.

The reasons for this are many and quite obvious to most of us. Dr. Poppel in his book on pancreatic disease pointed out that if we are going to measure this distance, we have to be sure that we are actually measuring it from the portion of the stomach that overlies the vertebra. Unfortunately, some stomachs may lie entirely to the left of the spine so that measurements are of relatively little value. He emphasized the importance of taking right angle projections without moving the patient, and then noting which portion of the stomach crossed the midline. In the lateral view, one can then measure the distance from the spine to that portion of the stomach which actually crosses the midline.

He felt that if this technic were followed, the rule of Engle and Lysholm was roughly true, but was not infallible and could give rise to false positive diagnoses.

I think the use of measurements and the demonstration of alterations in the surrounding duodenum can perhaps be refined even further. Abdominal viscera are certainly not fixed, as we all know. You put the patient on his left side or prone or supine, and they move around. So I think one should specify the position of the patient and take a right angle film without moving the patient. It may be that by the use of a left lateral decubitus position, one may demonstrate a pressure defect in the duodenum that may not be present in the supine position.

I would like to ask Dr. Deibert to tell us just how valuable these measurements have been to him, and whether they have really made the difference in diagnosing pancreatic disease or pancreatic enlargement in the absence of other significant findings.

A large duodenal loop again is misleading, depending on the bodily habitus. I do not feel that a large duodenal loop has much significance unless we can demonstrate a pressure effect on the medial border. Certainly some people have quite large duodenal loops without evidence of pancreatic disease.

I would also like to ask Dr. Deibert just what are his diagnostic criteria for the roentgen diagnosis of acute pancreatitis. Most of the roentgen signs are not specific. Although they may indicate an enlargement of the pancreas, the enlargement can be due to many causes.

Dr. Carroll, I think, has done us a very valuable service in bringing to our attention this rather rare and interesting anomaly of the pancreas and emphasizing its diagnostic criteria. I do agree that once one is aware of the condition and knows what it looks like, one can diagnose the disease. He is to be congratulated on his diagnostic acumen in diagnosing these cases.

One other question I would like to ask is whether he has ever seen a case of annular pancreas in the third portion of the duodenum. In one case of duodenal obstruction that was brought to my attention the surgeon, upon exploration, found pancreatic tissue in the duodenal wall and thought it was partly responsible for an obstruction of the third duodenum. I hate to be classed with the discussant who always has a slide in his pocket, but I do have one slide. A week after reading Dr. Carroll's paper, the following patient came in, and perhaps having learned a lesson from reading his paper, we made the correct diagnosis.

This was a 45 year old, man who consulted a

physician because of a 40 pound weight loss, several months of vomiting and mild upper abdominal discomfort. The gastrointestinal examination revealed partial obstruction of the midportion of the second duodenum due to a smooth annular constriction. At operation this proved to be an annular pancreas which was treated by partial resection of the constricting ring.

Dr. Deibert (closing). As you realize, I did not get through my slides. Some of this material will be published in the paper. I made quite an extensive study of this over a period of six years.

The measurements as Dr. Seaman indicated, are of little consequence. The diagnosis is a makeshift and a rehashing of the information from the clinician plus one's own suspicion of a lesion of the inner sweep of the duodenum. The disappearance of the postbulbar valvulae, associated with displacement are to be considered essential. I was aware of the discrepancies in measurements as described in the study you mentioned.

Dr. Carroll (closing). I would like to thank Dr. Seaman for his kind remarks. I do not believe I would have made the diagnosis in your case, Dr. Seaman, because there is not nearly as much dilatation of the duodenum as is usually seen.

I have seen three other cases of congenital annular pancreas that my colleagues have found and have been kind enough to show me. In none of our eight cases has the obstruction ever been in the third portion of the duodenum, and I do not believe it is possible for the usual anomaly to cause obstruction there.

I think also that a resection of the rim is usually not the surgical treatment of choice because of the danger of pancreatitis and because of the danger of recurrence of the obstruction following surgery.

Radiographic Diagnosis of Carcinoma of Head of Pancreas*

GLENWOOD L. COOK, M.D., *Laurel, Miss.*

The author calls attention to the distorted pyelogram which may result from pressure by pancreatic lesions.

THE PURPOSE of this article is to review the many conventional radiographic signs of carcinoma of the head of the pancreas and to present an additional sign found in the right pyelogram of a proven case with no demonstrable urinary disease. This pyelographic sign, which will be discussed later, is not diagnostic alone but should be considered with gastrointestinal signs already well established and easily recognized.[1-3]

The pancreas is probably one of the most difficult components of the digestive tract to evaluate radiographically, inasmuch as the organ is never visualized directly. However, many pancreatic diseases, including malignancy, may be detected by visualizing the pancreatic duct system following the injection of an opaque solution into the duct of Wirsung, but this procedure must be performed at operation.[4] The pancreas is fairly well fixed, being blocked by the duodenum on three sides, anteriorly by the stomach and posteriorly by the posterior abdominal wall. When the head is enlarged, as in carcinoma, the neighboring viscera are displaced, compressed or rearranged and the radiologist must rely on this altered anatomical arrangement in making a diagnosis. Due to the pioneer work of Whipple and his associates in resection of the gland for malignancy, much emphasis has been placed on the diagnostic signs in recent articles in spite of the high operative mortality in the few reported cures when a radical operation is performed.

Carcinoma of the pancreas is a rare neoplasm and, like other malignancies of the digestive tract, is more common in men than women. The incidence is 1 to 2 per cent of all cancers.[5] It occurs between the ages of 30

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and 70 years. The symptomatology is usually uniform with weight loss, epigastric distress, and persistent and increasing jaundice due to pressure on the common bile duct. When these symptoms appear in a male about 50 years of age and an organic lesion of the stomach can be ruled out, carcinoma of the pancreas should be suspected.[6]

Case Report

Case 1. A. E., a 43 year old, white male was admitted to the hospital on January 28, 1955, complaining of nausea, colicy abdominal pains, jaundice, light stools, dark urine and weakness of two months duration. He had lost 30 pounds of weight in the last six months.

Laboratory findings revealed a diabetic type of glucose tolerance curve with a fasting blood sugar of 111 mg. per 100 cc., serum amylase of 70 Somogyi units, icterus index of 43.9 which later rose to 95 and positive direct van den Berg test. The urine contained 2 plus bile but no red or pus cells. The blood count was normal except for secondary anemia.

The roentgen findings of the gastrointestinal and urinary tracts are reproduced in figures 1, 2, 3 and 4.

At laparotomy the head of the pancreas was markedly enlarged, irregular and hard but not adherent or fixed to the neighboring viscera. The gallbladder was normal in size but the common bile duct was dilated. A biopsy was taken following which a cholecystojejunostomy and entero-enterostomy were performed.

The histopathologic diagnosis was adenocarcinoma of the pancreas.

FIG. 1

Excretory pyelogram at end of 10 minutes. The right renal pelvis is thinned out and calyces obliterated by enlarged head of the pancreas (adenocarcinoma).

FIG. 2

Gastrointestinal study. The duodenal loop is widened and single arrow indicates a prominence of the ampullary region ("inverted 3 sign" of Frostberg). Double arrows indicate a compression of the gastric antrum ("pad" sign) by adenocarcinoma of head of the pancreas.

Pyelographic Findings

In a recent article, Chamberlin and Imber[7] presented a series of six cases showing changes in the left pyelogram in patients having either carcinoma or cysts involving the body and/or tail of the pancreas and with no demonstrable urinary disease. The pyelographic changes, they concluded, were the result of direct pressure of the body and tail of the pancreas which lies obliquely over the left kidney when the patient is in a supine position. In this position the pancreas is frequently under the costal cage and an enlargement will, by its weight alone, exert pressure upon the kidney. The pyleograms showed varying degrees of distortion and displacement of the collecting system.

The case presented here is similar except for location of the tumor; the head of the

pancreas was involved and the pyelographic changes were noted on the right. However, it is our opinion that these changes are brought about by the same mechanism, that is, direct compression of the kidney. Normally, the head of the pancreas lies in a midline position but, when enormously enlarged, the pressure exerted is in the line of least resistance, that is, toward the abdominal cavity and to the right. An excretory pyelogram (Fig. 1) taken at the end of 10 minutes reveals the renal pelvis to be thinned out and the calyces obliterated. A primary renal malignancy or other intra-abdominal or retroperitoneal tumor in the vicinity of the right kidney could produce a similar picture and every means should be used to rule out such a possibility. However, with other positive signs of pancreatic malignancy, the possibility of two primary malignancies seems unlikely.

Peripancreatitis, fixation of the kidney and compression of blood vessels causing impairment of renal function have been considered as contributory factors influencing the pyelographic changes.[8-10]

FIG. 3

Gastrointestinal study. Arrow indicates a postbulbar compression made by a dilated common duct.

FIG. 4

Gastrointestinal study shows anterior displacement of the stomach by adenocarcinoma of the head of the pancreas.

Gastrointestinal Findings

The gastrointestinal findings are well established and have been related many times.[1-3] Figure 2 illustrates the "inverted 3 sign" of Frostberg. The ampullary region is held stationary by the common duct while the duodenal loop above and below is widened by the tumor. The "pad" sign of the stomach is also observed, indicating a mass behind the stomach. Figure 3 shows a postbulbar compression made by a dilated common duct. Figure 4 shows anterior displacement of the stomach and again a widening of the duodenal loop is noted.

Summary and Comment

The pyelographic changes observed in carcinoma of the head of the pancreas, together with the conventional gastrointestinal signs, are presented. It is emphasized that the pyelographic findings are supplementary and not diagnostic alone, inasmuch as renal and other extrarenal malignancies may produce similar changes. A proven case is reported.

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Operation for Tumor of a Solitary Kidney*

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Fortunately tumor in a solitary kidney is a rare finding. When it does occur its management offers a problem to the surgeon.

CONSERVATION OF TISSUE has always been and always will be the objective of the surgeon in operative procedures on the kidney. Partial excision of localized pathologic conditions is accepted as the best procedure when the surgeon reaches the decision, from information gained from diagnostic data, that the particular lesion present can be completely excised and the remaining normal renal tissue, with its blood supply intact, can be preserved. Calycectomy, which is especially indicated in dilated calyces containing stones, is the best operation to employ when the remaining portion of the kidney, from pyelographic evidence, presents a normal appearance. Hemi-nephrectomy, especially in dealing with a pathologic condition of one portion of a reduplicated pelvis, has been a well recognized procedure when the other segment of the kidney is normal. However, in many cases, in spite of the accuracy of present-day diagnostic methods, the ultimate decision as to the appropriate procedure to employ in a given case must rest on surgical exposure of the organ and direct observation. Excision of localized tuberculomas has been advocated by Lattimer[1] and by various Scandinavian surgeons. Simple excision of serous cysts with preservation of the kidney is certainly preferable to nephrectomy.

When the contralateral kidney is absent, or its function so impaired that its ability to preserve life may be questioned, the necessity of using conservative methods is obvious, if surgical intervention is indicated on the better or only kidney. Any operation upon a solitary kidney must be considered with the utmost caution, and only undertaken with the hope of improving or, at least, conserving the function of the kidney upon which life depends.

Neoplasm of the kidney always has been and will be a mandatory indication for nephrectomy when the function of the contralateral organ has been proven adequate to preserve life. However, Vermooten[4] has advocated the excision of localized tumors if such a method is technically feasible and deserves credit for bringing to our attention that such a procedure can be carried out successfully. When a diagnosis of tumor in a solitary kidney has been made the prognosis is grave, and often, under such circumstances, with the thought that nephrectomy alone is adequate in dealing with a neoplasm, the opinion is given that any surgical procedure is contraindicated. It is

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true that in most instances of tumor arising in a solitary kidney, surgical exploration will reveal an inoperable condition, especially when the neoplasm is cortical in origin. Yet an occasional case will be encountered in which local excision of the neoplasm may be surgically practicable, and gratifying palliation at least may be obtained in an individual otherwise condemned to die.

In 1948, Ferris and Daut[2] reported the following case: A diagnosis of papillary tumor of the pelvis of the right kidney was made in a 61 year old man in whom the left kidney was absent. At exploration "a papillary epithelioma could be seen arising from the posterosuperior aspect of the renal pelvis and extending 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment of the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2 (Broders' method), with no obvious infiltration of the renal pelvis." The remaining portion of the tumor was thoroughly destroyed by electrocoagulation. There were no postoperative complications, but the blood urea concentration on discharge was 64 mg. per 100 cc. The patient remained well "until June, 1953, at which time he developed hematuria and hydronephrosis" and death, presumably from uremia, ensued.

In this interesting case excellent palliation was obtained for five years in a patient who, had operative exploration been denied, would surely have succumbed in a short time.

Gibson[3] has reported a patient 86 years of age who had profuse hematuria of 24 hours duration. He had had a right nephrectomy 14 years previously for papillary carcinoma of the renal pelvis. Diagnostic studies showed a large filling defect in his remaining kidney with secondary hydronephrosis due to partial obstruction at the ureteropelvic junction by tumor. At operation a pedunculated tumor the size of a walnut was excised together with a generous margin of pelvic wall around the origin. The ureteropelvic junction was restored by a pyeloplasty with polyethylene splinting and nephrostomy drainage. The pathological specimen showed papillary carcinoma, grade I. A postoperative pyelogram made before discharge showed no evidence of filling defect and the ureteropelvic junction showed no evidence of obstruction. The patient remained in good health and free from symptoms six months after operation.

Vermooten[4] reported in 1950, the case of a 52 year old woman with a diagnosis of tumor of the left kidney. At operation a tumor 10 by 7 cm. in size was found occupying the midportion of the kidney and apparently well encapsulated. The tumor was completely excised with a 1 cm. border of normal tissue, hemorrhage being controlled by a rubber-shod clamp placed on the vascular pedicle. Study of the excised tumor showed that it had been completely removed with a 1 cm. margin of normal kidney tissue. The diagnosis of clear cell carcinoma was made from the sections prepared for microscopic study. Fifteen months later the pyelogram was normal except for obliteration of the middle calyces, and there was no clinical evidence of recurrence and the patient was sympton-free. Two years and four months later chest x-ray showed three metastatic nodules in the left lung. These were excised with uneventful recovery. A left retrograde pyelogram at this time showed the kidney normal with normal function. Death occurred 8 months later from pulmonary metastases.

Case Reports

Our first case bears some resemblance to Gibson's patient. However, certain features of our patient's history and clinical course are so unique that they will be reported in detail.

Case 1. A 57 year old, housewife was first admitted on August 21, 1950, because of intermittent painless hematuria of five months duration.

In 1943, an abdominal hysterectomy had been done elsewhere for fibroids. Apparently the right ureter was injured and a ureterovaginal fistula drained for about four months. After the vaginal drainage of urine ceased, excretory urograms revealed no function of the right kidney; the left kidney was considered normal. The patient had no flank pain except for one episode of "right pyelitis" shortly after the hysterectomy. Until March, 1950, the patient was in good general health. At that time, she had an episode of painless hematuria lasting about eight hours.

A retrograde pyelogram at the left side revealed a filling defect in the lower portion of the renal pelvis. Five subsequent episodes of hematuria followed the initial one. Retrograde studies were repeated, revealing an apparent increase in the size of the filling defect. The patient was then referred for evaluation and therapy.

Physical examination on admission to The Johns Hopkins Hospital was essentially normal. The left kidney was palpable but nontender. The right kidney could not be felt. The hemogram and blood chemical

studies were normal. An occasional white cell and one to two red cells were seen in the centrifuged urine specimen. A trace of albumin was also noted. An intravenous urogram showed a filling defect in the lowermost portion of the pelvis and the lower calyx of the left kidney (Fig. 1). There was no function on the right side.

Operation. On August 23, 1950, through a left flank incision, a pelviotomy was performed and a raspberry-like sessile tumor was found. Cephalad to this tumor, a smaller pedunculated tumor was noted. Both tumors were excised with the cutting current. The bases were then thoroughly destroyed with the coagulating current. A 25 per cent solution of podophyllin on cotton swabs was then applied to the tumor-bearing area. The bleeding was well controlled and the pelvic incision was closed with a continuous suture of 4-0 chromic catgut. Two Penrose drains were placed at the pelviotomy site; closure was routine. The patient tolerated the procedure well.

The postoperative course was uncomplicated, except that the flank wound drained urine for four days. The patient then started voiding in good quantities. There were no significant changes in the blood chemical examination. She was discharged on the twelfth postoperative day in excellent condition, the incision firmly healed.

Pathologic Examination. Histologic examinatoin of the tissue removed revealed a papillary tumor composed of rather uniform, large cells arranged in sheets with scant cytoplasm and vesicular nuclei. Some of the fragments contain a few strands of smooth muscle

FIG. 1, CASE 1

Preoperative intravenous urogram. A filling defect is present in the pelvis and lower calyx of the left kidney, no secretion of the dye on the right side.

FIG. 2, CASE 1

Retrograde pyelogram of left kidney two years postoperative. The pelvis and upper calyces are well delineated without evidence of filling defect. The middle and lower calyces are faintly outlined; the calyces are cup-shaped, with no evidence of filling defect. Delayed filling of the lower and middle calyces is probably due to postoperative stenosis of the infundibula of the middle and lower calyces.

and connective tissue in which tumor cells are seen to grow. The final diagnosis was *papillary carcinoma* of the renal pelvis.

Clinical Course. Her subsequent course was followed closely by retrograde pyelograms. The films revealed no evidence of recurrence of the tumor. Some narrowing of the infundibulum of the inferior major calyx was noted shortly after operation, but this has remained unchanged in subsequent films (Fig. 2).

The patient returned on November 27, 1953, complaining of a mass in the right side of the abdomen which she had noted first three weeks previously. She was admitted to the hospital. The general physical examination was essentially normal. The left kidney was not palpable or tender. In the right upper quadrant, and extending to just below the umbilicus on the right, was a large, smooth, freely movable, nontender mass, about 12 cm. in length and 8 cm. wide.

The blood chemical studies and hemogram were entirely normal. The urine contained 15 to 20 red blood cells per high power field (after cystoscopy) and one plus albumin. Extensive radiologic studies were done which indicated that the mass was extrinsic to the bowel, stomach and duodenum, and did not involve the gallbladder. It was felt that the mass was most probably a large right hydronephrosis.

Operation. On December 12, 1953, an exploratory laparotomy was carried out through a right rectus incision. A brownish-blue retroperitoneal cystic mass

was immediately noted. Minimal dissection revealed that this was a hydronephrotic kidney with a greatly dilated tortuous ureter. The mass was aspirated and about 200 cc. of thick brownish fluid was removed. Nephrectomy and partial ureterectomy were carried out without incident. There was no evidence of intra- or retroperitoneal metastases. The left kidney felt normal. The patient tolerated the procedure well and had a benign postoperative course. She was discharged on the tenth postoperative day in excellent condition.

Pathologic Examination. The specimen consisted of a large hydronephrotic sac containing chocolate brown fluid, with virtually no remaining renal parenchyma. At the infundibulum of the superior calyx, there was a 2 by 2 cm. papillary tumor.

The histologic section shows a kidney pelvis in which there is chronic inflammation and thickening. Over a broad surface of the pelvis there is a papillary tumor, composed of fairly well differentiated cells piled up on slender connective tissue stalks. There is no direct invasion of the pelvis seen, although in a very superficial part of the mucosa directly beneath the tumor there are tumor cells within what appears to be a lymphatic. The capsule of the kidney appears normal, but the renal parenchyma is only one high power field in thickness. The final pathologic diagnosis was *hydronephrosis* with *papillary transitional cell carcinoma* with no direct invasion seen.

Comment. The first tumor of the renal pelvis in this patient was manifested by total gross painless hematuria. Routine urologic diagnostic technics completed the diagnosis. Since the kidney involved in tumor was the only one functioning, electroresection was used to remove the tumor. The invasion of the muscle seen in this tumor indicates it was a papillary carcinoma rather than a "benign papilloma."

The nonfunctioning right kidney was asymptomatic and not palpable for many years. Its sudden increase in size was alarming, but in retrospect probably represented hemorrhage from the tumor. If the tumor had not produced bleeding, its discovery certainly would have been greatly delayed. Since no invasion of muscle was seen in this second tumor, the diagnosis of papillary carcinoma is equivocal. The finding of tumor cells in a lymphatic, however, strongly suggests that the tumor is a carcinoma.

Case 2. H. R. N., a 46 year old man, entered the hospital August 26, 1947, with the complaint of hematuria.

Seven months previously he had sudden severe pain in the right lumbar region. Cystoscopic examination was done and he was told that he had an injury of his right kidney and that the left kidney was not functioning. A month later hematuria began to occur intermittently, and three months later the bladder filled with clots and became temporarily obstructed. Intermittent bleeding continued and two weeks before admission cystoscopic examination and retrograde studies were repeated. He was told that a tumor or a soft stone was present in the right kidney and that the left kidney was not functioning.

Physical Examination. On admission the patient was well developed and well nourished but appeared chronically ill. Blood pressure was 142/88. The examination was essentially normal except that the right kidney was easily palpable, seemed somewhat larger than normal, but was not tender. The prostate was normal. *Blood studies.* Hgb. 8.8 Gm. (60 per cent), white blood cells 6650, N.P.N. 48 mg. for 100 cc. The urine showed albumin 1+, sugar 0; the sediment was loaded with red cells, an occasional white and epithelial cell were found, but no casts nor organisms.

Urography. Intravenous urogram showed delayed excretion on the right side with marked hydronephrosis, and no excretion on left (Fig. 3). *Retrograde studies.* Catheters introduced into each ureter ascended easily to each kidney region. From the right there was profuse bleeding; the left was functionless. Retrograde pyelograms (Fig. 4). The right pelvis was not visualized, the opaque medium returning to the bladder without passing the ureteropelvic junction. On the left side there was a small, irregular deposit of the medium lateral to the upper end of the ureter which was visualized, but there was no evidence of pelvic or calyceal structures. Following this procedure, the temperature rose to 102.8° and the P.S.P. excretion was 25 per cent in 2 hours.

FIG. 3, CASE 2

Intravenous urogram, preoperative. Delayed function and marked hydronephrosis are present in the right kidney; excretion is insufficient to demonstrate any filling defect. There is no secretion on the left side.

FIG. 4, CASE 2

Bilateral retrograde pyelogram. The dye on the right side will not enter the pelvis of the kidney, flowing back along the catheter into the bladder. On the left side there is a small irregular collection of the medium at the upper end of the ureter, without evidence of pelvic or calyceal structures.

Operations. On September 3, under spinal anesthesia, the left lumbar region was explored in the faint hope that some condition, such as obstruction at the ureteropelvic junction, would be found and that by some plastic procedure the function of the left kidney might be restored. The ureter was exposed and followed up to a small mass of fibrous tissue at its upper end at which point the lumen became obliterated. No evidence of a kidney could be found and microscopic examination of the tissue at the upper extremity of the ureter showed fibrous tissue with a few ill-defined and poorly developed tubular structures.

On September 10, under spinal anesthesia, the right kidney was exposed through the usual lumbar approach in the hope that a pedunculated tumor of the pelvis might be found which could be destroyed through a wide pyelotomy incision. The kidney was found to be moderately enlarged, but its surface was smooth and no nodules were apparent. After isolating the ureter the pelvis was exposed and found moderately dilated and a soft mass could be felt. The pelvis was opened widely and a large amount of necrotic material, in some areas yellowish in color, extruded and was removed. The finger in the pelvis enucleated a large tumor apparently arising in the upper calyx. In most places it was necrotic; no definite pedicle was demonstrable. After all the palpable tumor tissue had been removed, the wall of the upper calyx, which was considerably dilated, felt smooth. Bleeding, which had been brisk, diminished markedly. The pelvis was irrigated with ether followed by salt solution in the hope that any remaining tumor tissue would be destroyed. A mushroom catheter was placed in the pelvis and the wound closed in layers in the usual manner.

The patient was returned to his room in good condition. There had been moderate shock during the bleeding which accompanied the enucleation of the tumor, but his blood pressure level was restored by transfusion of whole blood.

Pathologic Examination. Microscopic examination of the tissue showed *clear cell adenocarcinoma* (hypernephroma).

Clinical Course. There were no postoperative complications and the patient's general condition rapidly improved. The N.P.N. which had risen to 95 mg. fell to 27 mg. per 100 cc. and the P.S.P. excretion rose to 55 per cent in 2 hours. The pyelostomy tube was removed on the twentieth postoperative day and the wound healed promptly with no subsequent urinary drainage.

The nature of the tumor predicted a hopeless ultimate prognosis, because it would seem impossible to destroy a cortical tumor through a pyelotomy incision. For two months the patient continued to gain weight and strength, and was free from pain. The wound then became inflamed, urinary drainage began at the site of the tube, and the patient's condition deteriorated steadily until his death approximately four and a half months after operation.

Comment. In view of the nature of the tumor this patient's prognosis was absolutely

FIG. 5, CASE 2

Postoperative pyelogram through pyelostomy tube.

FIG. 6, CASE 2

Intravenous urogram three weeks postoperatively. Upper calyces are markedly dilated; middle and lower calyx do not fill, and there is a filling defect in the upper part of the pelvis.

hopeless. But exploration of the left kidney was considered justifiable for the reasons stated, and when the absence of any secretory renal tissue had been demonstrated, exploration of the right kidney was considered indicated because the nature of the tumor was not known. The operation was undertaken in the faint hope that a pedunculated papillary growth of the pelvis might be found and be destroyed by electrocoagulation.

Summary

Three cases have been recorded in the literature, in each of which a tumor was removed from the kidney. Two additional cases are reported, in both of which operation was performed for a tumor occurring in a single kidney. The result in one of these cases, in which a papillary carcinoma involving the pelvis and one calyx was excised, has been most satisfactory to date. The patient has been well for four and a half years without evidence of recurrence clinically or on radiologic studies. This successful result emphasizes the fact that patients having a single kidney which is suspected of harboring a neoplasm should be explored surgically, in the hope that a localized tumor, suitable for complete excision, may be found.

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Discussion (Abstract)

Dr. Edwin P. Alyea, Durham, N. C. Dr. Colston's subject brings to my mind three main points: (1) Operation on a solitary kidney; (2) resection or destruction of a malignant tumor in any kidney; and (3) resection or destruction of a tumor in a solitary kidney. As to the first point, operation on a solitary kidney,—these kidneys are of three kinds: (a) Congenital solitary kidney; (b) surgical solitary kidney; and (c) a normal kidney with a contralateral functionless kidney.

Not included in this discussion are surgical emergencies such as a stone blocking the ureter at the ureteropelvic junction of a solitary kidney. Operation then is a necessity, and such patients usually do extremely well. Our discussion considers what we might call "optional operations" on solitary kidneys.

At Duke Hospital in the past 20 years we have had 64 patients with a solitary kidney,—38 of them were congenital and 26 surgical. Of the 38 congenital solitary kidneys, only 2 were operated upon. Both had stricture at the ureteropelvic junction and Foley Y-plasties were successfully carried out. Of the 26 solitary kidneys because of surgical removal, 2 had optional operations. One was for a staghorn calculus in the middle and lower calyx, and the second for a group of stones in a dilated lower calyx. Each patient had a successful heminephrectomy and did well. These operations were carried out with the idea of preserving all possible renal function in the only kidney. We can expect equally as good convalescence from operations on a solitary kidney as in the patient with two kidneys, provided the kidney does not become anuric. That has not occurred in our few experiences. As to the second point, resection or destruction of malignant tumors in any kidney, is a moot question at the present time. Careful search was made in the Index Medicus for the last 8 years and the Journal of Urology since its beginning. Only two reports were found in the foreign literature of heminephrectomy for a renal tumor, with a normal kidney on the other side; one in "Archivos espanotes de urologia," 1951, and one report in the German literature of the same year. Dr. Colston mentions two other reported cases. In the Journal of Urology in 1950, Vermooten reported the removal of a well encapsulated hypernephroma. He believes that under certain conditions, namely a clear cell tumor which is well confined to a definite capsule, as hypernephromas usually are, and as distinguished from the infiltrating granular cell tumor of the medulla, tumors may be resected locally even though the other kidney is normal. I most emphatically do not subscribe to this since I am a pessimist

when it comes to malignant renal tumors. I have seen a small clear cell tumor of only 2 cm. in diameter, already metastasized. Admitting that renal tumors are fickle and unpredictable in their behavior, I firmly believe that nephrectomy is still the operation of choice. As to the third point in this paper, the resection or destruction of a tumor in a solitary kidney is an entirely different matter. Here, we are justified in an attempted removal or destruction of a tumor, if it is at all possible surgically. I might recommend this even if there is a solitary metastasis, for such have been known to regress after removal of the primary tumor. Heminephrectomy is the operation of choice, if the tumor is in a position favorable for such a surgical procedure. We must remember that one needs only one-fourth of a normal kidney for life.

As to the case presently under discussion, Dr. Colston is to be congratulated for his success in this undertaking, and also for bringing this procedure before the profession, as a possible aid in adding comfortable years to such a patient's life. Dr. Colston, of course, does not suggest that this patient is cured. From the type of tumor that it was, a papillary tumor of the pelvis, it is quite probable that it will be true to form and reappear elsewhere in the urinary tract. I cannot forget the patient who came to us with the kidney already removed because of such a tumor. During the next 5 years we have chased that tumor down to the ureter; later to the bladder, still later to the prostatic urethra, and finally to the bulbous urethra.

Thank you for asking me to discuss this paper for I consider it a distinct pleasure to discuss any paper of my past and present teacher, whom I hold in such high regard.

Dr. Charles Rieser, Atlanta, Ga. I want to cite a case that was presented at a recent meeting of the Georgia Urologic Association by Dr. Prince of Savannah. He had a lady with a solitary kidney, and the pyelogram showed a very typical deformity of a cortical type of tumor. This was four years ago. He did not operate upon the patient. He did yearly pyelograms and one could see that the tumor was growing, but the woman was up and about, taking care of her daily duties, had no metastases, and apparently was getting along well. That is just another way of looking at a solitary kidney with a cortical tumor.

The other thing I want to say, and changing the subject, is that it was 25 years ago at this meeting of the Southern Medical Association that Dr. Davis, of North Carolina, presented his work on the resectoscope.

Dr. A. Keller Doss, Fort Worth, Tex. About six years ago I had the opportunity to see a patient who came in because of a story of gross hematuria. Upon making an x-ray examination it was evident that he had a large staghorn stone in his right kidney with three large calculi in the right ureter, each about the size of one's thumb. There was a non-functioning kidney on the right and apparently a normal appearing kidney on the left in the excretion urogram. The patient was not bleeding at the time that he was seen in the office. Without going into further detail at the time or waiting for him to bleed again, we put him in the hospital rather promptly, feeling that this was one person to whom we could offer a cure.

A right nephrectomy was accomplished, the stones were pushed up into the ureter so they could be engaged easily and removed. The patient did well for a period of ten days, and then began to bleed freely. I felt and hoped that he had a granulomatous lesion in the lower third of his ureter, which was bleeding owing to the presence of these stones which had been present in the ureter for years.

Sure enough, when we had an opportunity to do a cystoscopy, after he got over his immediate postoperative course, the blood was not coming from his ureteral stump, as had been hoped, but was coming from the left kidney.

We followed the course of the patient through the next two years most carefully. Repeated efforts were made to determine whether or not tumor cells could be found in the urine. None were found on careful examination by an excellent pathologist.

Retrograde polyureterograms or excretion urograms were made every three months. Finally, I had the idea that possibly the patient had a pyelonephritis aggravated by vesical neck obstruction and possibly resection would help. So in desperation I did a transurethral resection which accomplished nothing except that he was able to void better, doing away with the moderate residual urine he had had.

He continued to bleed. About 18 months to two years after the initial nephrectomy I thought I saw a small area of calcification in the lower calyx of his left and only remaining kidney.

Three months later we did another excretion urogram or retrograde polygram, I do not recall which, and the thing was gone. KUB film showed no evidence of it, but there was at that time a questioned filling defect. The man was 68 years of age at this time. The N.P.N. was normal.

At operation there was demonstrated a dimpling in the lower pole of the solitary kidney. A partial nephrectomy was done. Fortunately, we happened to get proximal to the lesion. The tumor was a papillary epithelioma, grade II, arising in the lower calyx of the solitary kidney. A tumor thrombus was milked up from the ureter, through the pelvis and out through the incision.

The patient did fairly well. His N.P.N. went up to about 95 mg., and he was confused for a few days, but we finally managed to get him up and about. He lived happily for some two or two and a half years thereafter. He began to complain of pain shortly before death, apparently due to metastases to the cervical vertebra. At postmortem examination it was shown that the remaining half kidney was completely free of neoplasm, and there was no perirenal neoplastic tissue. However, there was evidence of metastasis up and down along the aorta, and metastasis to the cervical vertebra.

The interesting point about this case is that before we could establish a diagnosis of the cause of hematuria, the lesion had already obviously metastasized. We did effect a cure in that particular kidney, but had we been more fortunate earlier, we might have prolonged the patient's life. However, he lived some two years after a partial heminephrectomy. I thought you would be interested to know of a similar case.

Dr. Lytle Atherton, Louisville, Ky. How long will a

patient live after a tumor is identified in the kidney? Of course, we all know that the sooner a kidney is removed after the diagnosis is made, the more likely we are to obtain a cure. By the same token, I should like to mention briefly the case of a man who was first seen, about four or five years ago, because of hematuria. He was 68 years old when first seen. Twenty-nine years before he was kicked in the side by a mule. He had a little hematuria at that time which cleared up within a few days time. Within six months, he began to notice a mass in his left side, the side which had been kicked. This mass continued to grow until it became about the size of a large grapefruit. He paid little or no attention to it because it caused him no pain.

He went on for 29 years and then had profuse hematuria. He was going into the hospital when I saw him, and pyelograms were made, which showed that he had a large filling defect of a portion of the renal pelvis, which suggested a tumor. At nephrectomy he was found to have a clear cell carcinoma. He recovered from his operation quite satisfactorily, and within six months had multiple bone metastases.

The question that comes up is, how long after a tumor first becomes manifest will the patient live without any surgical intervention?

Dr. Otto J. Wilhelmi, St. Louis, Mo. I would like to ask Dr. Colston a question which has been annoying me for some time. Why is it that upon primary examination in some of these cases there is apparently only unilateral function without compensatory function in the good kidney, and yet upon a second examination, maybe a year or six months later, function is present in the supposedly functionless kidney? Is this a physiological dysfunction? I have never been able to explain this. I have had two such cases.

Dr. Colston (closing). I want to thank the discussants very much for taking so much interest in this case.

In regard to Dr. O'Brien's question, this woman was rather thin. We did resect the last rib and had as much exposure as possible. We opened the pelvis, which was dilated by a blood clot I suppose, and were able to see the tumor. I think it arose in the infundibulum and not in the calyx. I must say that we could not see a definite pedicle. I felt that. After all obvious tumor had been removed we coagulated what we thought was the pedicle.

I appreciate Dr. Alyea's summary of the situation. I would like to say that, of course, had there been a good kidney on the other side, I would have done a nephro-ureterectomy. That is the procedure of choice in dealing with papillary tumors of the renal pelvis, including, of course, a cuff of the mucous membrane of bladder wall around the ureteral orifice.

Dr. Wilhelmi, I have seen one case of what you describe. I cannot explain it. One instance we explained by reflex anuria, if there is such a thing, because the day following a retrograde pyelography there was no excretion on what afterward proved to be the good kidney.

I want to again express my appreciation especially of Dr. Doss's very interesting case. It certainly supports the idea I had in reporting this case, and that is when a diagnosis of tumor in a solitary kidney has been made, exploration is justified. This is time even though in a high percentage of cases the results of exploration will probably be disappointing.

Femoral Shortening by Step Cut Osteotomy and Intramedullary Nail*

ROBERT M. O'BRIEN, M.D., and
RICHARD E. LORD, M.D.,† *St. Louis, Mo.*

The authors have described their technic of shortening the femur for inequality in the length of the lower extremities. Their results in ten cases were satisfactory.

INEQUALITY of leg length is a common orthopedic disability. Its most frequent causes are upper or lower femoral ephiphyseal injury, bone tuberculosis, osteomyelitis and anterior poliomyelitis.

If the difference in leg length is one inch or less, no serious limp nor disability ordinarily results, and minor shoe adjustments will correct the discrepancy. If the difference is significantly more than one inch a distinct functional and cosmetic disability occurs. Its correction requires major alterations in shoes, including unsightly cork lifts. Uncorrected, it may produce backache, marked limp, and disability in standing, running and walking.

Femoral shortening has been accepted widely as a practical solution to difference in leg length, in selected full-grown patients. The disadvantages of this procedure are outweighed by its relative simplicity and the resultant short period of disability as compared to operations which attempt to lengthen the short leg.

The historical aspects and the fundamental orthopedic principles involved in this procedure were discussed in detail in an excellent review by Howorth[1] in 1942. That article should be read by everyone interested in the problem of unequal leg length.

Thompson, Straub and Campbell[2] in 1954 reported their experience with shortening procedures done by two methods. A previously described technic of oblique osteotomy with screw fixation and plaster spica immobilization had given good results. However, to shorten hospitalization and allow early ambulation, in their 11 most recently treated patients transverse osteotomy of the femur was done, followed by intramedullary rod fixation. A number of complications occurred, such as bending or breaking of the intramedullary rod, and these authors concluded that "oblique osteotomy with screw fixation . . . was preferable to transverse osteotomy with intramedullary rod fixation."

Using a slightly different technic, we have had a happier experience with intramedullary nails in femoral shortening operations, and this report is concerned with a method of femoral shortening used successfully in 10 patients treated in the St. Louis University Group of Hospitals from 1950 to 1954.

Rationale of the Method

The advantages of intramedullary nail fixation of properly selected fractures of the femur are widely accepted now, and scarcely need be mentioned. External fixation by plaster or traction splints is rarely needed; thus, hospital time has been reduced greatly. Ambulation with crutches is often possible within a week or 10 days.

Experience has shown that the fracture most suitable for intramedullary fixation is that at the junction of the upper and middle thirds of the femur. This then should be the logical site for osteotomy in femoral shortening since, here, fixation is best and union most rapid.

Short oblique fractures are well immobilized by an intramedullary nail. The step cut osteotomy, a modification of the oblique fracture, should give good immobilization and tend to prevent rotation of the fragments.

Our procedure consists of step cut osteotomy at the junction of the upper and middle

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thirds of the femur, combined with intramedullary rod fixation. The results have been gratifying to both patient and surgeon, and there have been no serious complications in the 10 cases so treated.

Indications For Operation

About 50 percent of our patients had low back pain resulting from pelvic tilt, and were relieved by altering the leg length difference with shoe corrections; however, major shoe alterations are unsightly and expensive. For this reason some patients sought an operative solution to their problem. Cosmetic considerations were important in other cases. In general, femoral shortening operations should be considered when leg length difference exceeds one inch.

Determining the Amount of Shortening Necessary

Scanograms were made to determine the exact difference in leg length. Pelvic tilt was corrected by blocks under the feet. Clinical trial with shoe lifts of various heights was the final factor in preoperative calculations of the amount of shortening to be done. It was found that in most patients complete equalization of leg length was undesirable from the standpoint of function and the patient's comfort.

Operative Technic

The only special instrument needed to avoid complications and to add to the ease of the procedure is a large blade for the electric saw. Early efforts without this blade not only prolonged the operation but were responsible for several of the minor complications encountered. This blade should have a diameter of three and a half inches and, preferably, should be attached to an oscillatory type of electric saw.

Either the anterolateral approach, as described by Henry, or the lateral approach may be used to expose the junction of the upper and middle thirds of the femur. We prefer the anterolateral incision. Calculation of the amount of bone to be exposed is necessary. This can be done by doubling the amount to be shortened and adding one inch to insure the proper amount of bone with which to work.

If the bone is to be shortened 2 inches, three holes are drilled in line, 2 inches apart, on the anterior surface of the femur (Fig. 1, A, B, and C). Then the holes are connected, using the electric saw, making sure that the oversized blade goes through both cortices. After that, the bone may be bisected at the middle hole. The step cuts are completed with the electric saw, alternately holding each end of the bone out of the wound. Care must be taken in using the saw not to extend the cut past the drilled hole, for this tends to weaken the base of the steps.

The largest nail diameter which fits snugly into both fragments at the osteotomy site is the size used. (Both the oLttes and Küntscher nails have been used in this series.) A guide wire is introduced into the proximal fragment and driven through the skin above the

FIG. 1

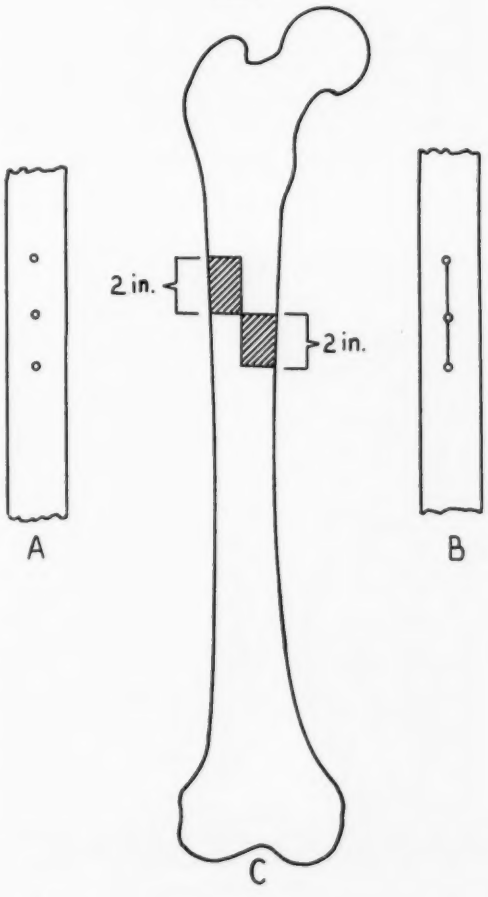

FIG. 2, A

Case 1. One day postoperative.

trochanter. The proper nail then follows the guide wire back to the osteotomy site, and the guide wire is removed. The steps are held together with a bone clamp and the nail driven into the distal fragment. Impaction may be necessary.

With the nail in place, the steps should cut out all rotation. If motion is present, small holes should be drilled through the steps and stainless steel wire sutures used to obtain firm fixation. Using the electric saw, the bone removed is cut into small matchsticks and placed around the area of the osteotomy. The wound is then closed in layers, and a snug elastic bandage is placed around the extremity from toes to groin.

Postoperative Care

Bilateral quadriceps exercises are started on the second postoperative day. Straight leg raising usually is accomplished by the seventh to the tenth day. Walking with crutches ordinarily is started on the tenth day. The patient is allowed to balance himself on the shortened leg, but not to bear more than one-third of his weight on this extremity. Full weight bear-

FIG. 2, B

Case 1. Five weeks postoperative.

FIG. 2, C

Case 1. Fourteen weeks postoperative.

ing is not advised until there is sufficient evidence of callus present in roentgenograms. The average time of ambulation with crutches was 17.5 days. The average hospital stay was 29 days. The average period before full weight bearing without crutches was 14.5 weeks.

Case Reports

Case 1. L. B., a medical intern 28 years of age, had sustained an injury to the lower femoral epiphysis of his left knee 16 years previously, resulting in premature closure of this epiphysis.

On June 5, 1952, the right femur was shortened one and three-eighths inches by a step osteotomy and Lottes intramedullary nail fixation. The patient was using crutches by the twelfth postoperative day and was discharged from the hospital on the twenty-third postoperative day, when he returned to work on the medical service. Enough callus was present at the end of the twelfth week to allow him to discard crutches (Fig. 2, A, B, and C).

Case 2. V. S., an 18 year old student, had had polio at the age of 5 years, with marked weakness of the right lower extremity.

On December 16, 1950, the normal femur was shortened two inches, using a step cut osteotomy and a Küntscher nail. He was up on crutches on the tenth postoperative day and was discharged from the hospital two and a half weeks later. X-ray films made 15 weeks after operation revealed enough callus for full weight bearing without crutches (Fig. 3, A, B, and C).

FIG. 3, A

Case 2. One day postoperative.

FIG. 3, B

Case 2. Three months postoperative.

FIG. 3, C

Case 2. Six months postoperative.

FIG. 4, A

Case 4. One day postoperative.

Case 3. D. T., an 18 year old male, had two inches of shortening as a result of an unilateral slipped femoral capital epiphysis at the age of 14 years.

On October 28, 1953, the normal femur was shortened one and three-quarter inches. The immediate postoperative course was marked by a cramping pain in the patient's thigh and knee on the shortened side. The pain subsided and the patient was started on crutches on the twelfth postoperative day, and was discharged from the hospital 3 weeks later. Crutches were discarded at 13 weeks, and at the end of 4 months the patient returned to work as a stable boy.

Case 4. O. M. B., a 17 year old female, had a short right femur as a result of an extensive osteomyelitic process at 6 years of age.

On July 20, 1950, the left femur was shortened one and three-quarter inches, using a step osteotomy and a Küntscher nail. Because rotation was still present at the osteotomy site after the nail had been driven, several strands of No. 28 stainless steel wire were run through drill holes in the area of the osteotomy and tightened. Walking with crutches was started on the seventh postoperative day and the patient was discharged from the hospital 3 weeks later. On her own responsibility, the patient began to discard her crutches after the eighth postoperative week (Fig. 4, A, B, and C).

Case 5. J. R., a 17 year old male, had been treated 5 years previously for a septic hip, and had a solid operative fusion.

On June 12, 1952, the normal femur was shortened

FIG. 4, B

Case 4. Two months postoperative.

FIG. 4, C

Case 4. Three and a half months postoperative.

one and three-quarter inches, using a step osteotomy and a Lottes nail. Walking with crutches was started on the twentieth postoperative day and the patient was discharged from the hospital 4 days later. X-ray films showed sufficient callus in 13 weeks to allow weight bearing without crutches.

Case 6. M. H., a 16 year old female, had Ollier's disease involving the lower shaft of the left femur.

On April 24, 1952, one and a half inches were removed from the shaft of the right femur, using a step osteotomy and a Küntscher nail. While the nail was being driven into the distal fragment, it encountered the anterior cortex and became firmly embedded in it. Neither mechanical ingenuity nor brute force could extract the nail. X-ray examination showed the nail to be in the cortex two and a half inches below the osteotomy site, but it did afford good fixation at the area of the steps. The protruding part of the nail above the greater trochanter was cut off with a bolt cutter and the wounds were closed. The patient was placed in balanced suspension for 5 weeks and walking with crutches was started the seventh week. Full weight bearing was started the eleventh week and crutches were discarded completely the eighteenth week.

Case 7. A. C., a 21 year old woman, with an old tuberculous hip, had undergone many operative procedures before solid bony fusion was obtained.

On July 19, 1952, three inches of the normal femoral shaft were removed, using a step osteotomy and Lottes intramedullary nail. Fixation was incomplete, so a one and a half hip spica was applied. Three weeks later a walking spica was applied and was worn 3 weeks. The patient was allowed to discard crutches in 17 weeks from the time of operation.

Case 8. B. F. M., an 18 year old female, had had extensive osteomyelitis of the right femur.

On November 13, 1952, two and three-quarter inches of the left femur were removed, using a step osteotomy and a Lottes nail. The diameter of nail used did not fix the fragments well, and one week after operation the fragments separated. A closed reduction was done and a spica was applied. The patient was up on crutches in three and a half weeks and crutches were discarded in 13 weeks.

Case 9. F. M. T., an 18 year old girl, had polyostotic fibrous dysplasia and numerous fractures through the left femur.

On January 7, 1954, a step osteotomy was attempted, removing two inches from the normal femur. Due to the absence of the large saw blade in the operating room that morning, the osteotomy was attempted by using a smaller blade and an osteotome. The smaller blade did not reach both cortices and, on using the osteotome, the lower step was broken off at its base. At that point it was decided to turn this into an oblique osteotomy, and this was fixed with the intramedullary nail. Walking with crutches was started the eighth postoperative day, and she was discharged from the hospital one week later. Crutches were discarded at 13 weeks and the patient was allowed to return to work three and a half months after operation.

Case 10. F. S., a 19 year old male, had a left hip fusion in treatment of tuberculosis.

On December 28, 1950, two inches of the femoral shaft were removed. A step was broken off during the procedure, but the short oblique osteotomy was fairly stable. Walking with crutches was started the thirteenth postoperative day. Weight bearing without crutches was allowed 14 weeks after operation.

Complications

It will be noted that both patients who required plaster spica immobilization were those who had the greatest amount of bone removed, that is, two and three quarter inches and three inches respectively. The power of the muscle to hold the bone fragments together decreases in direct proportion to the length of bone removed. A highly equivocal figure as to the amount of bone that might be removed safely by this procedure is three inches.

In the two instances where the steps of the osteotomy were fractured at the time of surgery, an electric saw blade of ordinary diameter was being used. Use of the blade of extra large diameter plays an important part in the ease of operation and helps to avoid unnecessary complications, as it will cut through both cortices of the bone.

In all cases, an attempt was made to make the osteotomy site the junction of the middle and upper thirds of the femur. In some patients, the middle third was the site. Both these areas have healed well but, due to the better nail fixation with the upper site, we believe it is the level of choice. At any site, obtaining freedom from rotation of the fragments seems to be a prime factor in rapid union.

TABLE 1

SUMMARY OF CASES

No.	*Patient*	*Operative Shortening*	*Follow-up*	*Ambulated with Crutches*	*Hospital*	*Ambulated without Crutches*
1.	L. B.	1⅜ in.	22 mo.	12 days	23 days	12 wks.
2.	V. S.	2 in.	40 mo.	10 days	27 days	15 wks.
3.	D. T.	1¾ in.	5 mo.	12 days	37 days	13 wks.
4.	O. M. B.	1¾ in.	45 mo.	7 days	30 days	16 wks.
5.	J. R.	1¾ in.	22 mo.	20 days	24 days	13 wks.
6.	M. H.	1½ in.	24 mo.	46 days	54 days	18 wks.
7.	A. C.	3 in.	21 mo.	23 days	36 days	17 wks.
8.	B. F. M.	2¾ in.	17 mo.	24 days	45 days	13 wks.
9.	F. T.	2 in.	4 mo.	8 days	14 days	13 wks.
10.	F. S.	2 in.	41 mo.	13 days	(other surgery)	14 wks.
	Average	2 in.	24 mo.	17.5 days	29 days	14.4 wks.

TABLE 2

SUMMARY OF CASES

Average age	19 years
Oldest patient	28 years
Youngest patient	17 years
Average shortening	2 inches
Greatest shortening	3 inches
Least shortening	1⅜ inches
Ambulation with crutches	
Average	17.5 days
Earliest	8 days
Latest	46 days
Ambulation without crutches	
Average	14.4 weeks
Earliest	12 weeks
Latest	18 weeks
Delayed union	0
Nonunion	0
Infections	0
Average follow-up	24 months

Summary

1. Between 1950 and 1954, 10 patients at the St. Louis University Group of Hospitals have undergone femoral shortening procedures using a step osteotomy and fixation with an intramedullary nail (Tables 1 and 2).

2. Shortening has ranged from one and three-eighth inches to three inches.

3. It has been found that the greater the length of femoral shaft removed, the greater the incidence of complications. This procedure has been found very useful for removal of between one and three inches of bone.

4. The most common operative complication (2 cases) was that of fracture of the base of the steps of the osteotomy. This is easily avoided by using the oversized saw blade and is remedied, if it occurs, by converting the step osteotomy into an oblique osteotomy.

5. Postoperative plaster immobilization has not been necessary except for a walking spica in 2 cases. Both those patients had the maximum amount of shortening (two and three-quarter inches and three inches respectively). In each of these cases a satisfactory result was obtained.

6. No delayed unions, nonunion nor infections have occurred.

7. It is our belief that step osteotomy and intramedullary nail fixation offer the following advantages:

(a) Good stability

(b) Protection against rotation at the fracture site

(c) Assurance that the proper amount of bone has been removed.

(d) Desirable amount of bony contact

(e) Minimal interference with normal function of the affected extremity, diminishing tendencies to muscle atrophy and joint stiffness.

8. Economic loss has been held to a minimum. An average hospital stay of 29 days and an average time of discarding crutches in 14.5 weeks were very attractive to patients contemplating this procedure, as most of them were wage earners or students.

Conclusion

Femoral shortening by step cut osteotomy and intramedullary rod fixation is a safe and precise surgical procedure. It should be done more often, especially for shortening in the range between one inch and two and a half inches. As the amount of bone removed approaches three inches, technical difficulties increase and external fixation may be needed in some cases.

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Postoperative Infection of Intervertebral Disc Space*

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Infection in the intervertebral disc space may be the cause of persistent and severe sciatic pain.

WHEN FRANK and overwhelming wound infection occurs following disc operations, the diagnosis soon becomes obvious to all concerned. An unusual type of infection, concealed in and confined to the intervertebral disc space, can occur following operation upon the disc. In such a case, weeks or months may elapse before the diagnosis can be made and proper treatment be carried out. In this paper we wish to report four cases of the latter and outline the treatment which we follow in such cases.

Disease of the intervertebral disc following lumbar puncture has been reported by Pease,[1] Billington,[2] Downing[3] and others. In these cases, often in children, collapse of the disc followed puncture, and it may be assumed that in some of these infection occurred. This was probably true because the lumbar puncture was followed by much back pain, a febrile course, and development of sclerosis of the adjacent vertebral bodies which indicated a low-grade infectious process. In none of these infections of the disc was an operation done nor were cultures obtained. When such a complication develops after lumbar puncture, the treatment of choice has been rest, immobilization in a plaster jacket and antibiotics.

Ghormley,[4] in 1939, reported a group of patients having infections of the spine, including brucellosis, in which the infection appeared to localize in the disc and involved the adjacent vertebral bodies, with collapse of the space and destruction followed by reactive sclerosis and spurring of the vertebrae. Included also were infections of the disc following lumbar puncture.

Turnbull,[5] in 1953, reported three cases of infection following operation for intervertebral disc lesions. In one a psoas abscess developed whch was drained, and in another purulent fluid was drained from the disc at re-operation.

More recently Kern[6] described a case in which a disc operation was followed by a spinal fusion. A minor infection developed which was treated by aspiration of the fluid material in the wound. The patient did well for two and one-half years and then suddenly developed a high fever and meningitis. His wound was opened and pus drained from the fusion area. Osteomyelitis had been present and dormant until the meningitis developed. This patient expired following a convulsive episode.

In well over 1,500 operations for intervertebral disc lesions in the lumbar region, carried out on the Orthopedic services of Barnes, Jewish, Missouri Baptist and City Hospitals in St. Louis in the past 12 years, there have been three deaths and an infection rate of less than 1 per cent. One death early in the series occurred following a gross wound infection with septicemia before antibiotics were available. In this case the infection developed while the surgeon (J.A.K.) was out of the city and the wound was not opened until his return seven days after the operation. The second death followed a brain abscess which developed from a purulent meningitis resulting presumably from a lumbar myelogram, since autopsy showed no evidence of infection in the disc space or in the operative wound. The third fatality resulted from circulatory collapse following hyperthermia in a 72 year old man who was a poor operative risk. His

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operation was done under local anesthesia (by L.T.F.), and death occurred eight hours later. Autopsy revealed no conclusive cause of death.

In this series of cases there have been four problem cases of low-grade hidden infection in the intervertebral disc space, three of which developed postoperatively after removal of a pathologic disc. In the first case the wound healed after slight serous drainage. In the other two, the wounds healed cleanly and per primum. All three cases were given chemotherapy or antibiotics after the original operation. We believe this to be an important factor in localizing the infection to the intervertebral disc space. The other important factor, in our opinion, is the poor blood supply which is present in the intervertebral disc space. These cases are being reported because they proved to be difficult problems to the authors, and it is hoped that our experience may be of some benefit to others. Routinely our disc operations are done under local anesthesia and the wounds washed out with warm sulfonamide solution before closure and this was the procedure with the cases reported here.

Case 1. J. R., a 53 year old white male, was seen in consultation at Jewish Hospital by one of us (J.A.K.) on January 2, 1945.

He gave a three year history of low back pain, occurring in intermittent episodes. His last attack, two weeks previously, was accompanied by severe sciatica on the left side. He was unable to get out of bed, straight leg raising was limited on the left side at 10 degrees, and there was tenderness in the left buttock and over the fourth lumbar space. No reflex changes were present. The remainder of the physical examination was negative except for a few crepitant rales in the right lower lobe of the lung. Laboratory studies were normal except for a two-plus albuminuria and a slight bacilluria. Preoperative x-ray studies of the lumbar spine showed slight hyperthrophic changes.

FIG. 1, CASE 1

A B

Anteroposterior and lateral films of lumbosacral spine on March 5, 1945, after the first operation and before the second. No bony destruction is seen.

On January 10, 1945, under local anesthesia the fourth lumbar and lumbosacral discs were explored, and at each space a soft bulging disc was found and removed. The disc material was described as soft and necrotic in each space.

Postoperatively the patient developed temperature spikes as high as 102°F. On the fourth postoperative day he was placed on sulfadiazine therapy. His temperature became normal and remained so after the tenth hospital day. There was slight serous drainage from the wound, but it healed and the drainage ceased. The patient was discharged on the seventeenth day to convalesce at home.

The patient was readmitted to Jewish Hospital on March 17, 1945. He had done fairly well at home until March 15, 1945. At that time he developed severe left sciatica, back pain and fever. His temperature on admission was 101°F. and rose to 104°F. during the first day. The incision was tender, but there was no local redness, heat or swelling; straight leg raising was positive, neurologic examination was negative. Crepitant rales were heard at the base of the right lung. A blood culture was taken and grew out *Staphylococcus aureus*. Penicillin therapy was instituted and the fever diminished, but the back and sciatic pain continued. X-ray examination of the lumbar spine was as before except for slight narrowing of the disc spaces and for defects in the lamina of the vertebrae which had been operated upon (Fig. 1).

Because of continued back and leg pain, the lumbosacral area was re-explored on April 4, 1945. No infection was found until the fourth lumbar disc space was entered. As would be expected numerous adhesions were present. Upon opening this lumbar disc space pus was found. This disc was curetted gently, and the wound was thoroughly irrigated. It was then closed with catgut; a small vaseline gauze drain was left extending down to the infected disc.

Prior to operation the leukocyte count was 10,900 with a differential count of 65 per cent segmented cells, 6 per cent stab cells, 6 per cent large monocytes, and 23 per cent lymphocytes.

The patient was given penicillin therapy. The drain was removed after 48 hours. His pain diminished, the wound healed, and he returned home about two weeks postoperatively. Culture showed the material from the disc to contain *Staphylococcus aureus*.

Shortly, thereafter, he developed a severe recurrence of low back pain and left sciatic pain and was readmitted to Jewish Hospital. The wound was healed. The white blood count was 7,900. A lumbar myelogram was done for the first time and showed an indentation defect on the left side at the fourth lumbar space. X-ray study showed further narrowing of the fourth lumbar disc space.

The lumbosacral region was explored a third time on May 17, 1945. The fourth disc was sealed over. When this was incised there escaped a small amount of thin, relatively clear, fluid which contained a few small flakes which appeared to be fibrin. The space was curetted gently, but repeatedly, and the wound was irrigated and packed open with vaseline gauze. Culture showed hemolytic *Staphylococcus aureus*.

Pain was relieved. The wound filled in slowly and healed by secondary intention.

X-ray examination of the lumbar spine three years later showed a narrowed disc space with bony fusion of the fourth and fifth lumbar vertebrae on the left side across the facets and by a large dence osteophyte (Fig. 2).

Case 2. J. B., a 44 year old, white male of Italian extraction, was first seen in the office on September 23, 1949.

He gave a history of one episode of low back pain nine years previously. Five months before being seen he injured his back while lifting a 50 pound carton. No litigation was involved. There followed low back pain, and three weeks previously he developed left sided sciatic pain to the ankle.

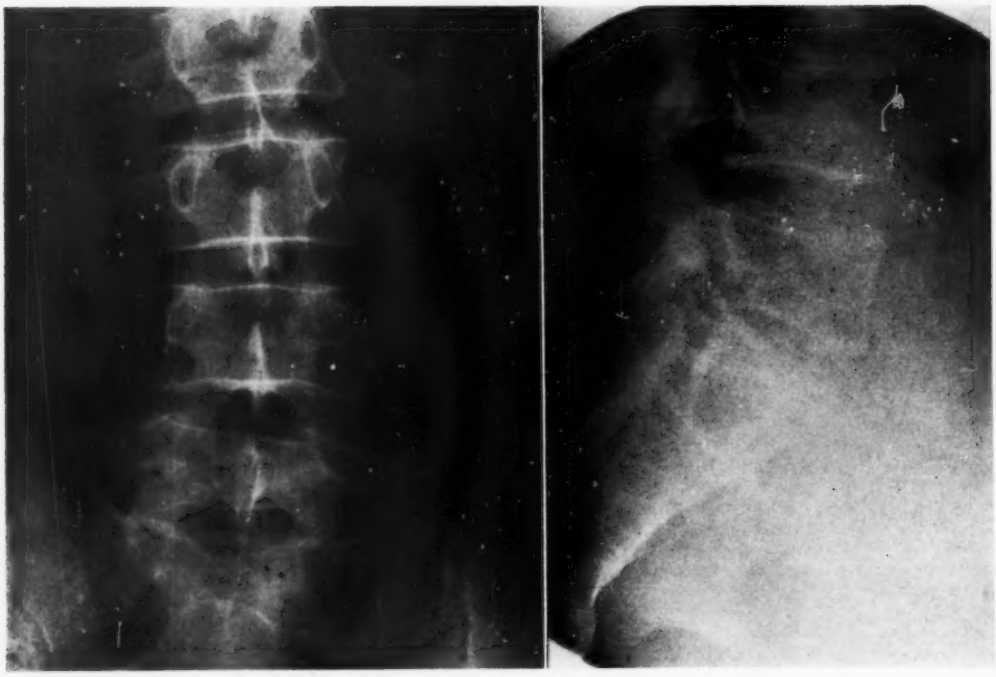
Examination showed a marked list forward and to the right. He was unable to bend backward or to the left. No reflex change was present. Hypesthesia was present over the lateral aspect of the left thigh. Straight leg raising was positive at 45 degrees on the left and 85 degrees on the right. There was tenderness over the left calf, thigh, buttock, and over the fourth lumbar space. The radiograph was negative except for a slight scoliotic curve (Fig. 3).

Conservative measures had not helped so the patient entered Barnes Hospital on September 30, 1949. A lumbar myelogram showed a large indentation defect between L-1 and L-2 on the right side. The Pantopaque was not completely removed. Spinal fluid protein was 48 mg. per 100 cc.

FIG. 2, CASE 1

X-ray film was made three years after the last surgical procedure. There is bony bridging with sclerosis of the fourth and fifth lumbar vertebrae on the left side.

FIG. 3, CASE 2



A B

Anteroposterior and lateral x-ray films of lumbosacral spine before first operation are negative except for a scoliotic curve which was due to muscle spasm. In the lateral view there was shown loss of normal lumbar lordosis.

On October 4, 1949, the fourth lumbar and lumbosacral discs were explored on the left side under local anesthesia (by L.T.F.). The lumbosacral disc was normal. The fourth lumbar disc was protruded far laterally under the apophyseal joint and was removed. The lateral position of the protrusion accounted for the myelogram being negative in this area.

The postoperative course was distressing to all concerned, and especially to the patient. His temperature was 38.9°C. the first day but was never over 37.5°C. after the second day. He was treated prophylactically with penicillin after operation. The wound healed per primum and sutures were removed on the seventh day. He developed a stiff neck and severe lumbar and left sciatic pain. In the second week he began to be seized with "spasms" of pain in his back and would scream out with each spasm. On October 13, 1949, a lumbar puncture showed a normal cell count, and a protein of 130 mg. per 100 cc. Culture was sterile. Various opiates and sedatives and intravenous Novacain did little to control his excruciating pain. Large doses of Tolserol did not control his muscle spasm. His back was manipulated under anesthesia without benefit.

In desperation, the back was again opened on October 14, 1949, thinking that a second disc lesion at the first lumbar level might account for his severe pain. The disc at this level was found to protrude in the midline. It was exposed from each side and removed. The first lumbar root on the left was taut even after removal of the disc and it was sectioned. He convalesced with somewhat less pain and was allowed to go home, still recumbent, on October 30, 1949.

He continued to have fairly severe pain in the lower back and left lower limb. He was unable to get out of bed and lost 12 pounds of weight.

On November 24, he was readmitted to Barnes Hospital for study. He had a low grade fever, never over 38°C. White blood count and differential picture were normal. Sedimentation rate was very rapid (1.2 mm. per minute). Agglutinations for brucella, typhoid, paratyphoid, and tularemia organisms were negative. Lumbar puncture showed normal pressure and counts; spinal fluid protein was 47 mg. X-ray study showed widening of the fourth lumbar disc space with destruction of the adjacent vertebral bodies; slight sclerosis was also present. Residual Pantopaque was seen.

On November 27, 1949, he was again operated upon by J.A.K. Many adhesions were present at the fourth lumbar space on the left. This disc was sealed over. Upon opening it, a closed cavity was entered which contained fluid, small bits of granulation tissue, and necrotic nuclear cartilage. The space was gently curetted, powdered pencillin was placed therein and a small vaseline gauze drain was left in the space.

The wound was closed and the drain removed 48 hours later. The wound healed cleanly. Cultures were sterile.

Postoperatively there was only slight fever for a few days. He was kept on penicillin therapy for several weeks. The pain lessened slowly and he began to improve, gaining 17 pounds of weight before discharge on January 15, 1950.

When last examined in August, 1953, he reported no back or leg pain unless he became too active or lifted very heavy packages in his work as a produce merchant. There was some numbness in the left thigh and his libido was poor (due to section of the first lumbar root). His last x-ray films in August, 1952, showed collapse of the fourth disc with near fusion of the fourth and fifth lumbar vertebral bodies by large dense osteophytes (Fig. 4).

Case 3. C. G., a 55 year old white lady, entered Barnes Hospital on November 4, 1949, because of a partial paralysis and pain in the right lower limb.

She had been injured in a fall in July, 1948, when she struck her right shoulder. About eight months prior to admission, she developed pain and numbness in the first and second toes of the right foot. Section of an interdigital nerve had given no relief and the patient had developed progressive paralysis with foot-drop. She had worn a drop-foot brace for two months. One and a half months before admission, because of pain in the calf, fever and chills, the patient was thought to have developed thrombophlebitis.

In 1941, carcinoma of the vaginal wall had been treated by radium implants.

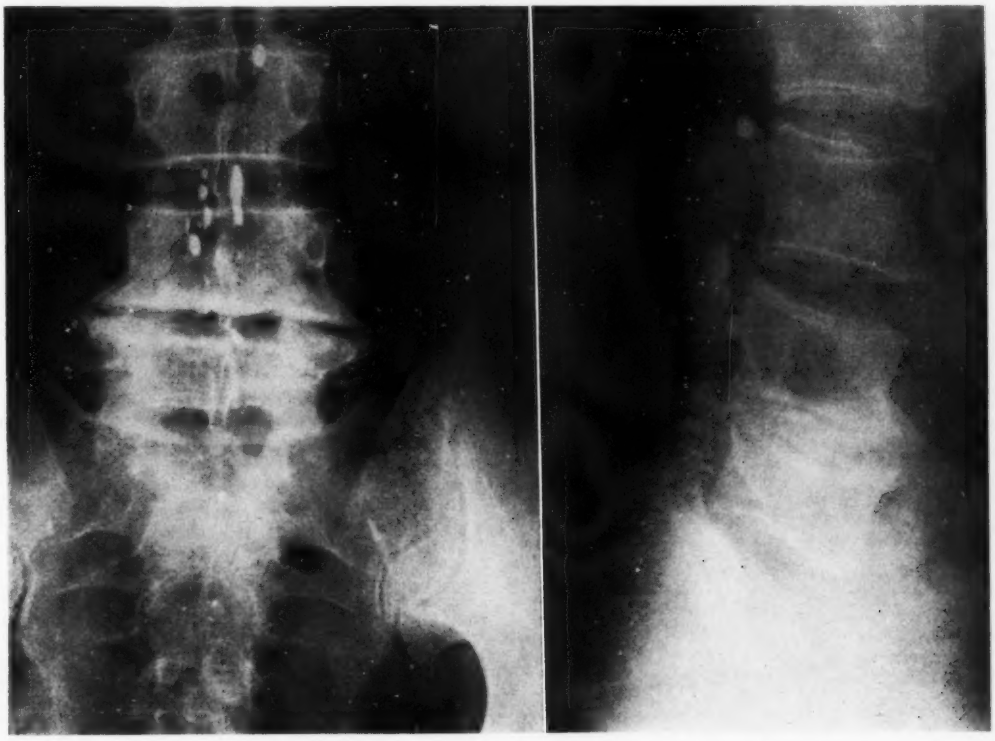
The right ankle jerk was absent. There was hypesthesia over the fifth lumbar and first sacral dermatomes on the right side. Straight leg raising was positive at 45 degrees on the right side and there was tenderness over the fourth lumbar and lumbosacral disc spaces.

A myelogram showed obliteration of the root sleeve at the lumbosacral and fourth lumbar level on the right (Fig. 5). Spinal fluid protein was 48 mg. per 100 cc.

On November 8, 1949, under local anesthesia, the lower lumbar area was explored on the right side (by J.A.K.). A large bulging disc was found and removed. The third lumbar and lumbosacral discs were normal. Sections showed moderate degeneration of the nuclear cartilage.

On the third day the temperature reached 40°C. Treatment with penicillin was begun. A blood culture

FIG. 4, CASE 2



A B

Films made three years following acute infection in fourth lumbar disc show more narrowing, with massive osteophytes which cause near-fusion of the fourth and fifth lumbar bodies.

showed *Staphylococcus aureus*. The white blood count rose to 13,000; the sedimentation rate was very rapid. Since urticaria developed while on penicillin, she was treated with sulfonamides and the temperature gradually subsided. The wound healed per primum but there was continuing low back and right sciatic pain. The patient was discharged on December 11, still with some pain and no change in the paralysis.

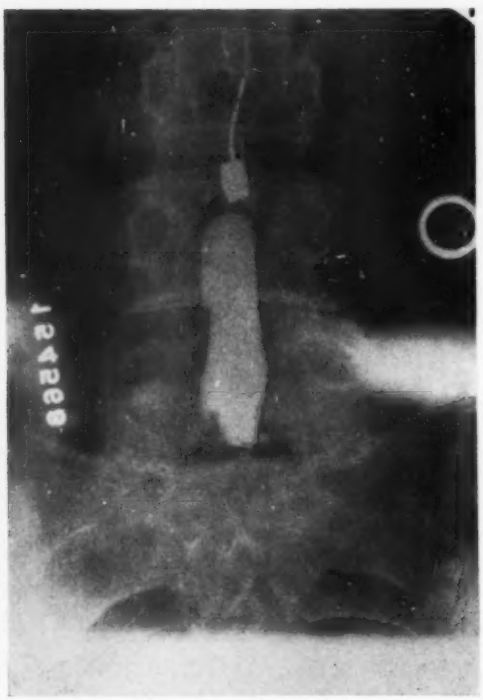
She remained bedridden at home and was readmitted to Barnes Hospital on April 3, 1950. In addition to back and leg pain, she now reported recent vaginal bleeding.

Examination of the back revealed straight leg raising of 5 degrees on the right side with a total peroneal palsy, and fixed contractures of the foot. A fixed pelvic mass was present on the right.

X-ray films showed collapse of the fourth disc space with bony destruction of the adjacent vertebral bodies; some sclerosis was present. A destructive lesion was present also in the right ilium (Fig. 6).

On April 5, 1950, the fourth lumbar disc was explored on the right side (J.A.K.). The nerve root was adherent and the disc space was closed by fibrous tissue. When the space was entered it was found to contain fluid, granulation tissue, and some very soft, necrotic disc material. The disc was curetted gently, the wound was irrigated with sulfonamide solution, a drain was placed in the disc space and the wound closed about the drain. The wound healed cleanly. Culture of the disc space gave no growth.

FIG. 5, CASE 3



Preoperative myelogram shows failure of the root sleeves of the fifth lumbar and first sacral roots on the right to fill with Pantopaque.

The pain in the back was somewhat less but the paralysis remained unchanged. The metastatic lesion in the pelvis was treated with deep x-ray. Neurosurgical consultation was obtained for consideration of a cordotomy but the patient decided against this. She left the hospital on May 29, 1950, her general condition slowly declining. She expired later that year from metastatic carcinoma, nine years after treatment for the primary lesion.

In spite of the negative culture from the disc material obtained at the second operation the postoperative course, x-ray findings and operative findings were so typical that this is believed to have been a surgical infection. It is believed that extension of the tumor in the pelvis was responsible for the foot-drop which developed later, and it is possible that this tumor, which was not diagnosed until the second admission, was responsible for some, if not all, of the pain and disability. However, at neither operation was there any evidence of a tumor mass encroaching upon the vertebral canal or nerve roots.

The following case is included in this series because the infection which developed in the disc space was similar in nature and was treated similarly, the difference being the manner of introduction of the infection.

Case 4. S. S., a 44 year old white man, entered Barnes Hospital on August 8, 1953, with severe lumbar pain radiating to each hip. Twenty-eight years previously he had injured his back in a fall, and one year before admission injured it again in an automobile accident.

In April, 1953, he had developed an "acute abdomen" and laparotomy had been advised. Repeated attempts to perform a puncture for spinal anesthesia were unsuccessful and general anesthesia was finally used. An acutely inflamed appendix, according to the patient, was removed.

Postoperatively there was much lumbar and hip pain. He had been disabled since his operation. Pain was aggravated by motion, coughing and sneezing. He denied fever or chills, but had lost 25 pounds of weight since the operation.

Examination revealed a healed abdominal scar. The upper lumbar spine was quite tender. No neurological changes were present. Straight leg raising was positive at 60 degrees on the right. His white blood count was 14,000, with 61 per cent segmented cells; sedimentation rate was 22 mm. in one hour. X-ray films showed narrowing of the second lumbar disc with bony destruction, and slight sclerosis of the adjacent second and third vertebral bodies.

On August 18, 1953, the second lumbar disc was explored from the left side by Dr. Robert Ramsey. He found dural adhesions and a bulging second lumbar disc. Inside the disc space was frank, yellow, purulent material with areas of granulation tissue in the disc. The space was curetted and closed without a drain. Culture revealed a paracolon bacillus, sensitive to Aureomycin, Terramycin and streptomycin.

Postoperatively the wound healed but became

FIG. 6, CASE 3

Films made five months after first operation, and just before the second one for drainage of the infected disc. The destructive area in the ilium on the same side, at the sacroiliac joint, is quite evident.

swollen and fluctuant. A hematoma was aspirated and the same organism again recovered. The postoperative course was moderately febrile. There had been no fever preoperatively after admission to Barnes Hospital. The patient was placed in a back support and kept on antibiotics on an outpatient basis. His last x-ray examination in February, 1954, showed collapse of the second disc space with sclerosis and spurring, and probable interbody fusion. X-ray films also suggested similar changes were taking place at the fourth lumbar disc with development of a large spur anteriorly there.

The patient has since made a complete recovery.

Discussion

It is possible, after operation for an intervertebral disc lesion, for a lowgrade infection to develop in, and remain localized to the intervertebral disc space. Development of such a complication must be kept in mind as a possibility when a patient develops undue back and sciatic pain with or without a febrile course following a disc operation. The presence of a cleanly healed incisional wound does not rule out the possibility of infection of the disc space. The infection may either be dormant for a while, or may be masked sufficiently to be undetected for weeks or months. We believe that antibiotics are to a large degree responsible for this masking, and that without them these cases might have been fulminating operative wound infections. Once the presence of such an infection is evident or is strongly suspected, we believe a second operation is indicated for evacuation and drainage of the intervertebral disc space. The second operation may be undertaken in an effort to relieve persistent pain and disability, and infection may not be suspected.

If evidence of infection is found in the disc, the posterior portion of the annulus should be opened widely. Particular care should be taken not to tear or incise the dura. The disc space should then be curetted gently but thoroughly, and the wound irrigated with a warm sulfonamide solution. Penicillin powder

should then be placed in the disc space and a small vaseline gauze or rubber tissue drain be left in the infected area and led out through the wound. The wound should then be closed in layers and general antibiotic and supportive therapy continued. In all of these cases the operation for drainage was not performed nor was the infection suspected until weeks or months after the primary procedure. If we suspect a wound infection during the period of primary healing we open and drain the wound immediately, evacuating any hematoma which may be present and start intensive antibiotic therapy.

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Discussion (Abstract)

Dr. Don H. O'Donoghue, Oklahoma City, Okla. When I received the program and saw the title by Drs. Ford and Key, I wrote them about a patient whom I was currently seeing who seemed to fit into their discussion. They kindly asked me to add this additional case to the list.

This white man, aged 35, followed the usual clinical course and was diagnosed as having a ruptured disc. He was operated upon for ruptured disc in November, 1950, at which time a large extruded disc was found at L-5 on the left side and a bulging annulus at L-4 on the left side. It was found that the spinous process and arch of L-5 were completely separate and that he had a spondylolisthesis. This arch was removed. Following this, a bone grafting was done, using a large H-block from L-4 to the sacrum supported by multiple cancellous strips and cancellous crumbs from merthiolated bone from the bone bank.

He had a completely uneventful recovery, was in the hospital 14 days, and was allowed to go home for bed rest and support by an ordinary corset for two months. At four months postoperatively, he had a mild complaint of back pain. The graft seemed to be satisfactory. There was no leg pain. At five months postoperatively, he had some pain in the left groin. He was examined by his local physician who told him he had some involvement of the ilioinguinal nerve and advised bed rest. By six months postoperatively he was complaining of pain in the left hip. Two months later, he was examined by us, and x-ray films showed the bone graft apparently doing well. The H-graft block was not entirely assimilated but did not appear to be sequestrated. He did have some local swelling over the wound so the wound was opened and subcutaneous granulation was found in which were several sutures. These were removed. There was no trace of any deep sinus at this time, nor did he have any sign of trouble. Meantime, he had been at work for four months, having gone back to work four months postoperatively. One year postoperatively, he was apparently entirely cured. He had no clinical symptoms, was doing his regular work and had no complaint.

Following this, his course was followed by his home doctor. In October, 1952, two years postoperatively, he developed weeping lesions of the scrotal skin and also a pilonidal cyst. The local physician removed the pilonidal cyst which healed uneventfully. He later developed pain in the right groin. This was incised and drained, gross pus being obtained. He later had a draining sinus in the left groin. These two areas were diagnosed as "buboes" and they persisted in draining. This was felt to be from a lymphadenitis due to the infection on the scrotum. He was sent to me for re-evaluation to see if there was any connection between his present condition and the "industrial illness" for which he had been treated two years before. There was a question as to whether or not the industrial case should be reopened on this basis. X-ray films showed some suggestion of sequestration in the H-block graft although there was no other evidence of any involvement around the low back other than the apparently healed spinal fusion. However, we injected the local sinus with lipiodol obtaining the pictures shown in the accompanying cut (Fig. 1, A and B). The lipiodol went up the psoas sheath as far as the front of the vertebra at the lumbosacral joint, then passed to the back of the vertebra through the intercorporial space where it curved laterally, passed over and down a portion of the psoas sheath on the opposite side. There was no question as to

FIG. 1, A

Lipiodol injected into the left inguinal sinus, shows anterior pooling and filling of the sinus on the opposite side.

FIG. 1, B

Lateral projection shows anterior pooling.

what he had,—an abscess in the space between the fifth lumbar vertebra and the sacrum. Operation was advised. A posterior approach was used. There was a solid spinal fusion, being particularly strong on the right side, and there was no motion between L-4 and the sacrum. The H-block was found to be sequestrated and was removed. Under the H-block was found to be a sinus on the left side, going down to the area between L-5 and S-1, also into the area between L-4 and 5. After injecting dye through a small catheter in the sinus at L-5 and S-1, we were able to recover the dye from the anterior draining sinus at the time of the operation. After removal of the H-block, curettement of the sinus and drainage of the wound, complete recovery ensued, and he has had no further trouble.

This case I think illustrates the necessity for very careful analysis of the patient's condition before one assumes that it was not caused by a prior operation. While this patient apparently had a good recovery from his back troubles, there is little doubt that the several incidents during his postoperative course were caused by the low grade infection in the intervertebral space. A gross injustice would have been done this patient had a careful analysis not been made and the patient properly treated.

I am sure this condition that Drs. Ford and Key have described is much more frequent than has been recognized. I certainly intend to study my own cases much more carefully in the future. I want to express my appreciation to them for their very excellent presentation.

(Since the above discussion, I have seen two additional cases of this same type of interbody infection with persistent symptoms. No bone from a bone bank had been used in either case.)

Dr. Elias Margo, Oklahoma City, Okla. I wish to add to this discussion by reporting three such cases of infection in the intracorporal space following disc fusions. Our three cases behaved very similarly to those reported in this paper and only one of the three was drained. In this case, it became very acute and drainage was obtained through the wound by reopening the wound after two to three days of very high temperature. A seropurulent material was obtained from the disc space but no organisms could be grown from the culture. He was placed on antibiotics and responded satisfactorily. The other two cases were treated conservatively with antibiotics and have done very well, going into a solid fusion with the exception of one who is still complaining. This is a compensation case and the patient probably complains a great deal more than would be expected in the average case.

Whiplash Injuries*

E. G. LIPOW, M.D., *Washington, D. C.*

This type of injury to the neck is common in automobile accidents and not infrequently is overlooked. Its recognition is important not only to prevent more or less permanent organic sequelae but to prevent also the initiation of a psychoneurosis.

NOT TOO LONG AGO many injuries now known as "whiplash" were labeled neck sprains. They were often allowed to become chronic. Because of the paucity of x-ray and objective findings these conditions often never were cured. The patient lost faith in his doctor, the physician became impatient and another so-called psychoneurotic was made. In 1934, Lonnerblad[1] described a "hurling back" symptom complex in which "pain between shoulder blades, rupture of the trapezius and of the rhomboids, and fractures of the spinous processes of cervical vertebrae" was found. He felt that this was a trade injury in heavy manual labor. In 1940, the "clay shovellers" fracture[2] was described and it is interesting to note that in the discussion of the diagnosis of this entity the author stated, "In the majority of cases the provisional diagnosis has been muscle strain. In only one case was this condition, that is, avulsion fracture of tips of the spinous processes, suspected, and in that case, the patient was not a "clay shoveller." In a discussion of fractures of the cervical vertebrae, Eastwood in 1940[3] stated that in his own belief the common acute torticollis following muscular effort is entirely a muscular condition in no way caused by minor displacements of the articular process. The "cervical syndrome" was ably described by Jackson[4] in 1949, and a regimen of treatment was proposed. She stressed that treatment must be individualized and stated that conservative, nonsurgical treatment gave the best results. Meyers[5] later concluded that most causes of the cervical syndrome are sequelae to whiplash injuries and felt that most symptoms are manifestations of cervical root pressure. In an excellent article Gay and Abbott[6] made observations upon the long period of disability considering the mild character of the accident. Gershon-Cohen[7] and his associates duplicated the stretching of the interspinous and nuchal ligaments in cadavers. With a continuing increase in automobile accidents in which the whiplash injury occurs, a more vigorous approach to the diagnosis and treatment of this condition is desirable.

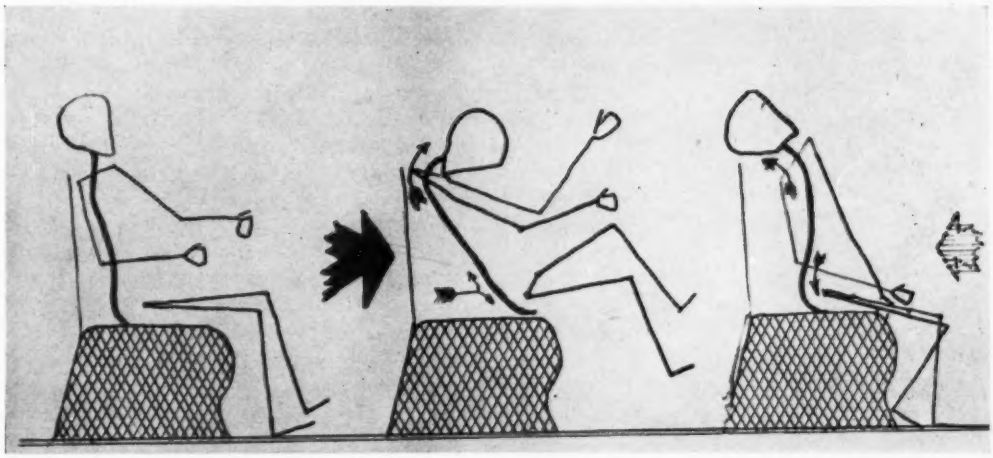
Mechanism of Injury

A whiplash injury is the forceable flexion of the cervical spine following a sudden acceleration forward from a position of rest and the attending elastic rebound with consequent hyperextension (Fig. 1). It usually happens when the automobile in which the patient is sitting at rest, stopped for a traffic light, or the like, is hit from behind with force. It can also occur when a vehicle stops suddenly and the patient is thrown forward. In these cases the forces which cause this injury are hyperextension, then an overcorrected whiplash hyperflexion. Other causes are a violent slap on the back, clipping and body blocking in football, and falling down steps or escalators, etc. However, by all odds, the commonest cause is the collision from behind. In 50 consecutive cases, collision from behind with a stopped vehicle in front was responsible for 78 per cent (Table 1). The greatest amount of flexion and force is found in the so-called movable portions of the spine, i.e., the cervical and the lumbar. We feel that most of the symptoms that we have followed stem from injuries in and around C-3 to C-5 and L-4 to L-5. This is simply our impression based on clinical findings. The 50 cases reported in this paper were selected because of the, (1) lack of roentgenologic findings other than straightening of the cervical curve, (2) minor or complete absence of any associated previously existing conditions, in the neck or back*, and (3) absence of a history of any similar injury of this type prior to the one reported.

*Read before the Section on Orthopedic and Traumatic Surgery, Southern Medical Association, Forty-Eighth Annual Meeting, St. Louis, Mo., November 8-11, 1954.

*As osteoarthritis or narrowing of intervertebral spaces in the neck or back.

FIG. 1



Mechanism of the injury. The large black arrow represents the initiating force, the white arrow the force of the elastic rebound, and the line arrows indicate the direction and site of the stresses on the spine.

Anatomy

Appraising the anatomical factors involved in whiplash injury, it is important to remember that the skeletal structure holds in fine balance the musculature of the neck. The atlas permits flexion and extension while the axis permits rotation of the atlanto-axial joint. The medulla and the cervical cord lie in this vertebral column of the atlas, the axis and the five adjoining cervical vertebrae. Practically all the innervation of the muscles involved in these injuries arises from these segments of the cervical cord. The joints of the cervical vertebrae are of the diarthrodial variety. They allow simple gliding motions. There is a joint cavity surrounded by a distinct articular capsule, lined with synovial strata.

The ligamentum flavum consists of yellow elastic tissue and is a powerful agent in maintaining curvature of the vertebral column. It extends from the anterior surface of one lamina, the posterior surface of the lamina next below and thus bridges the potential gap between the laminae of adjacent vertebrae. The other important ligament of the neck besides the ligamentum nuchae is the weak intraspinous ligament.

TABLE 1

ACCIDENT FACTORS

Exciting Factor				
Collision from rear and side rear	39	78%	Number of patients	50
Sudden deceleration (sudden stop—bus, streetcar, escalator)	7	14%	Male	27
Miscellaneous	4	8%	Female	23
			Youngest	19
			Oldest	63
			Av. age	37.8

The musculature of the neck is quite complex. Many of the true back muscles are composed of numerous converging and diverging fascicules and should be grouped in one functional sense rather than in subdivisions of component groups. The superficial layer is represented by the trapezius arising from the superior nuchal line and ligamentum nuchae, which itself consists of extensively developed cervical supraspinous ligaments. The second layer is formed by the splenius capitus and levator scapuli muscles. Just beneath these are found the rhomboids and the long back muscles, the longissimus and the iliocostalis. Underneath these muscles, below the superior nuchal line, are the muscles connecting the occiput to the upper cervical vertebrae, the rectus capitis posterior, major and minor, and the superior and inferior oblique capitis muscles. It is thus seen that the origin and the insertion of most of these muscles is either in or close to the occiput. Therefore it is not at all surprising that occipital headaches are common following this injury. The prevertebral muscles are the longus coli which bends the neck forward, the longus capitus which bends the head forward, and the intertrans-

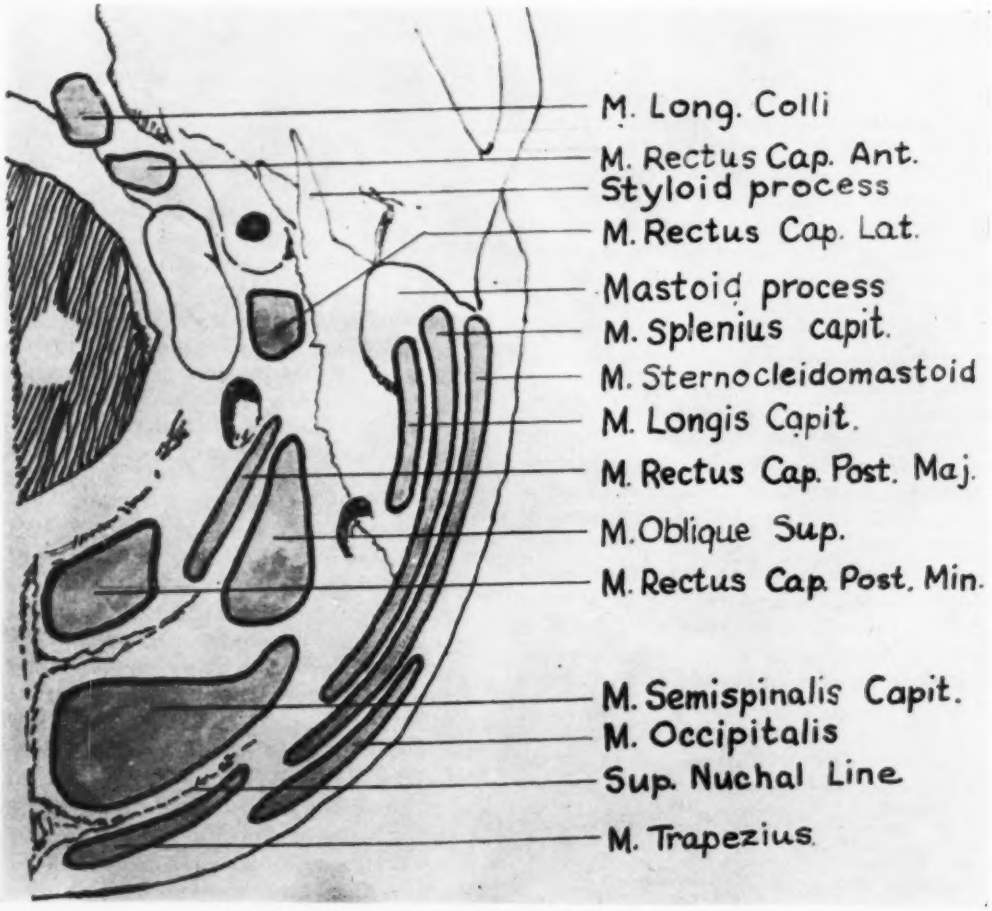
verse muscles, seven pairs of small, fleshy strips which connect and bind the extremities to the cervical transverse processes (Fig. 2).

The innervation of most of the structures involved in whiplash injuries arises from the cervical and brachial plexus, from the spinal accessory nerve, the eleventh cranial nerve, and separate segmental peripheral nerves. Segmental pain about the shoulder, neck and upper extremity, due to peripheral cervical nerve root irritation, is so distributed that occipital pain is from C-3. Pain along the vertebral border of the scapula may be due to irritation of C-4. Pain in the shoulder and upper arm is related to C-5 and C-6, and in the hand to C-7 (Fig. 3).

Pathology

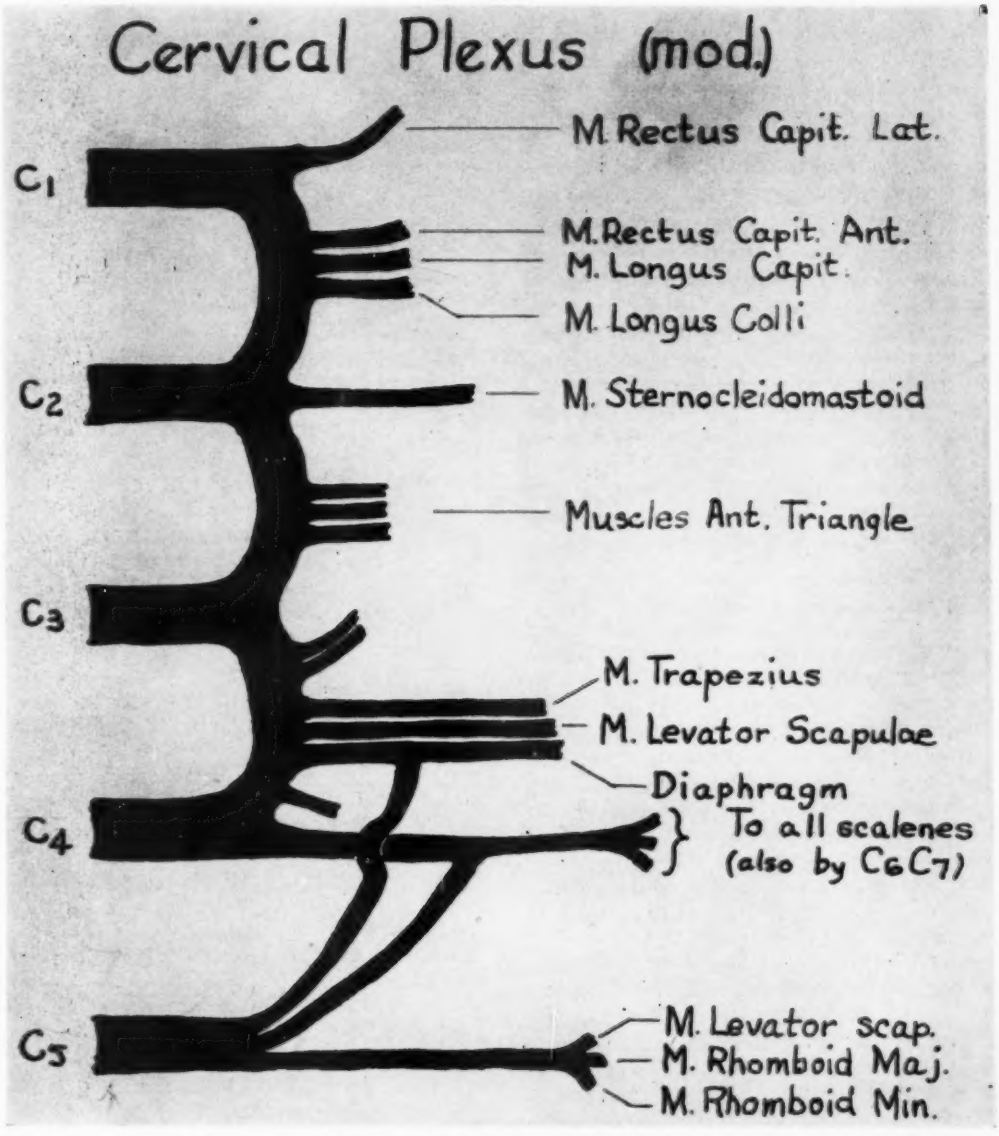
The pathological findings following the injury consist essentially of disruption of the normal anatomy by avulsion, fracture, hemorrhage, laceration and encroachment on the normal structures. Hemorrhage can occur in the soft tissues of the neck and around the nerve trunks. A permanent arrest of bleeding may be accomplished by the formation of an inflammatory exudate consisting mainly of lymph which in due time becomes firmly organized and converted into granulation tissue. This causes adhesions and pain because of proximity to the peripheral nerve fibers. Partial avulsions and ruptures of the muscles and tendons of the neck can occur, and when

FIG. 2



Muscle insertions on the external surface of the base of the skull.

FIG. 3



Schematic representation of the cervical plexus.

healing does take place the muscles may remain incompletely healed or partially replaced by fibrous tissue. The tendon rupture may show bridging by tendon tissue but with the bridging and healing there is often shortening. Because of the mechanism of the injury, traumatic cervical radiculitis is not uncommon. Edema is present and pressure from this source in or around the neuralforamina will cause a moderately long continued nerve irritation. Avulsion fractures of the spinous processes, fractures of the articular facets, and dislocations of vertebrae also occur. In this paper we are limiting our discussion to the so-called cases showing a negative x-ray picture, except for unusual straightening of the

normal curvature, and in which bony disease is absent. It is, however, of great moment whether there has been previous disease of bone, such as osteophytic changes, arthritis, or destruction of the intervertebral cartilage with consequent narrowing of the intervertebral space. Under such circumstances it is obvious that the symptomatology and, indeed, an exacerbation of a previous condition can be a serious complication.

Concussion is interpreted as a sudden mechanical deformity which results when the forward movement of the brain is suddenly arrested against the anterior wall of the cranium and this condition may further cloud the picture.[6] If the injury is severe enough, and the mechanism of the injury is such as to cause protrusion of the nucleus pulposus, symptoms of cervical disc will be found. When all of these injuries are essentially untreated, a condition of the cervical syndrome is reached which, of course, is sometimes most difficult to treat.

Symptoms and Course

Following an accident such as previously described there may be a period of unconsciousness and/or a dazed feeling for varying periods of time. Soon afterward the patient complains of pain and stiffness of the neck with a more or less constant occipital headache which may radiate toward the frontal region and often around the eye (suboccipital nerve) (Table 2). The pain in the back of the neck becomes more intense and spreads down the lateral aspect of the neck to one or both shoulders. Rotation of the head and flexion of the neck and head becomes limited due to pain and spasm. The pain and stiffness in and around the shoulder may become more severe, with extension to the elbows and fingers. This is often accompanied by paresthesias. Pain in the upper chest and in the costosternal junction is sometimes present

TABLE 2

SYMPTOMS (Cerebral)

	Yes	*None*	*Percentage*
Unconsciousness	5	45	10
Dazed	13	37	26
Headaches	42	8	84
Nausea	19	31	38
Depression	15	35	30
Psychoneurosis	15	35	30

TABLE 3

SYMPTOMS

	Yes	*None*	*Percentage*
Spasm (post-occipital, shoulder muscles)	42	8	84
Pain			
Neck	48	2	96
Scapulae	43	7	86
Shoulders	45	5	90
Upper-back	33	17	66
Mid-back	11	39	22
Low-back	16	34	32
Upper arm	19	31	38
Elbow	6	44	12
Fingers	2	48	4
Chest	18	32	36
Paresthesias	18	32	36

and occasionally there is difficulty in swallowing. Torticollis ensues and stiffness and pain in the shoulder then is associated with limitation of motion. Numerous areas of tenderness and trigger points appear within twenty-four hours and are easily found on palpation. This part of the syndrome resembles rotator cuff lesions, bursitis, shoulder-hand symptoms, and, indeed, patients have been treated sometimes for these conditions with but little relief (Table 3). As the condition progresses the headaches continue and the patient becomes apprehensive and even psychoneurotic. Often symptoms of concussion and the postconcussion syndrome color the general picture. If concomitant conditions (especially those due to the accident itself), such as lumbosacral strain, with or without sciatic components, are present, the whiplash injury symptoms may be bypassed in treating the other injuries. Associated injuries, such as sprains, fractures, and contusions, add to the confusion and must also be treated. Pre-existing conditions, such as osteoarthritis, tension states, cervical disc syndromes, scalene anticus syndromes and the various neuritides are aggravated. Prolonged convalescence and delayed cure result. X-ray films usually show no specific findings and but little bony disease though straightening of the normal cervical curvature is present in many instances.

Diagnosis

The diagnosis is facilitated by rather negative roentgenographic findings as described above. It is made by the history and the constant findings of occipital headaches, spasms of the trapezius or supraspinatus muscle groups, points of tenderness and trigger areas

of the trapezius, along the vertebral border of the scapula, and tenderness on the lateral aspect of the neck. The unusually long time to recover from a rather mild accident, out of all proportion to the objective findings, is outstanding in this syndrome. In a rather typical case, the history is the biggest clue to the diagnosis, associated with the length of time before this seemingly trivial injury disappears (Table 4).

Treatment

The treatment of whiplash injuries must be directed toward the elimination of the most important symptoms; hence, the elimination of spasm of the neck and shoulder muscles is imperative. Heat used in its various modalities, such as hot packs, luminous heat, infra-red, short wave and microtherm therapy, is useful. This is followed in most cases by cervical traction either in the hospital, office, or home. If used in the hospital, with complete bed rest, five to twelve pounds are usually used more or less continuously twenty-four hours a day. The traction is only removed for eating and for unnecessarily long-continued discomfort. In the office, Sayre overhead traction to 60 pounds is applied for short periods, very much as used for the cervical syndrome by Martin and Corbin.[8] This treatment is supplemented at home by head traction up to 15 pounds. Each case is highly individualized and the length, duration, and the amount of traction is adjusted for each patient. We have not had to use a Thomas collar in the reported cases, though the Lewin collar[9] at the beginning of treatment has been used with much comfort for the patient.

Muscle relaxants of the mephenesin group are well tolerated, useful, and have been used in every one of the cases reported. When spasm was severe, and in cases of bed traction, repository tubocurarine, Tubadil, was employed in 1 to 2 cc. doses intramuscularly with excellent results. Analgesics, such as aspirin and codeine, were used in early phases of treatment in many cases. As soon as spasm was controlled, it was seldom found necessary to continue any other analgesics except aspirin and then only for headache. Sedation by means of the barbiturates was used sparingly, usually only for a few days immediately following the injury. As soon as the emotional strain following the accident was lessened, the sedatives were used only at bedtime for sleep (Table 5).

TABLE 4

Onset of Symptoms	Immediate	Within 6 hours	Over 6 hours	24 hours and longer
(length of time following accident)	29-58%	15-30%	6-12%	8-16%
Time Treatment Started	Immediate	Within 6 hours	Within 12 hours	Within 24 hours	Over 2 days
	17-34%	4-8%	12-24%	9-18%	8-16%

TABLE 5

TYPE OF TREATMENT USED

	No. Cases	*Percentage*
Muscle relaxants (oral-mephenesin, etc.)	50	100
Tubadil (repository tubocurarine)	17	34
Cervical traction	42	84
Procaine injections	26	54

Procaine injections, 10 cc. of 1 per cent solution in acutely tender areas and in the trigger points, were used in 26 cases (52 per cent). When these tender points are made less painful, spasm is more quickly eliminated and recovery is definitely hastened. In some cases paravertebral cervical blocks were done but, since the tender areas generally were found in the trapezius and supraspinatus muscle attachments and attachment to the scapula of the rhomboids, cervical blocks were not necessary. Following these injections paresthesias were often eliminated in the upper arm.

In every instance the case was fully discussed with the patient and the neurologic symptoms and the depressive state explained. The patient was encouraged to help the physician and in most cases was glad to do so and felt that he had a part in curing himself. Only two patients were regarded as developing such strong psychoneurotic tendencies that the services of a psychiatrist were required. In the other instances the patient became adjusted rather early to his injury, and in only 6 cases (12 per cent) did we feel that the psychoneurosis, which was mild, was unimproved after we thought there had been other maximum benefits in management.

Periods of observation of these patients ranged from one week to 54 months, during which time an assessment of improvement and/or cure was made. The cases reported as *improved* are those in which the patient only

occasionally referred to a passing stiffness or mild transitory headaches without any disability or loss of work. Those reported as *cured* denied all of these conditions. The period of disability or absence from work speaks for itself. It is obvious that there is considerable individual variation in these periods, inasmuch as they range from zero days to 90 days. The time lost from this so-called trivial accident is not to be taken lightly. An average time loss of 14.8 days per case is a distinct economic hardship. We have found that the time lost from work varies inversely with the time treatment was instituted after the accident. There are individual variations, of course, but on the whole the rule works out rather constantly. It was also noted that the number of treatments varied directly with the severity and extent of the injury but was even more closely related to the time treatment was begun after the accident. The sooner the treatment was started the sooner the patient got better. Eighty-four per cent of our cases started treatment within 24 hours, and it is encouraging to note that we found approximately 88 per cent were either cured or improved after a period of management. One of the two patients mentioned previously as being rather severely psychoneurotic following this accident did not report for treatment until nine days after the injury (Table 6).

Medicolegal Implications

In many cases of whiplash injury, compensation and litigation procedures affect the patient's real and apparent recovery. Too often the victims of the usual type of accident (collision from behind) have been told by friends and attorneys that they "were in the right and are entitled to damages." They are often encouraged to continue to complain to build up a bigger demand for compensatory emoluments and, unless this particular factor is kept in mind and the patient's clinical progress is carefully evaluated, unnecessarily prolonged treatment may result. This may subsequently in itself lead to a mild depression or even a psychoneurosis. Malingering may be attempted and it is indeed a difficult situation to determine where the real complaints leave off and conscious exaggerations begin. Complete records and progress notes are of great value in dealing with this problem, and make reports and court procedures less troublesome and arduous, not to mention the help in treating the patient which, of course, is our primary object. Some method of evaluating disability in this condition, both during the active stage and the residual state, if any, should be devised and agreed upon between the responsible parties.

TABLE 6

	Most	*Least*	*Average*
Time lost from work	90 days	0 days	14.8 days
Number of treatments	87	2	10.6
Length of observation	54 months	1 week	30 months
	Cured	*Improved*	*Remained same*
Results	12-24%	32-64%	6-12%

Prognosis

The prognosis of this type of injury is, on the whole, good. Even if mild depression develops the outlook is not unfavorable provided treatment is begun early. It must be pointed out, however, that unrecognized cases may lead to protruded or degenerated intervertebral discs, to chronic strain, so-called fibrositis or myofibrositis of the posterior neck, shoulder and upper back muscles, unhealed fractures of the spinous processes and traumatic segmental chronic radiculitis. Even rather severe psychoneuroses out of all proportion to the clinical findings have been reported.[6] It must be remembered, however, that a cure can be expected if proper treatment is started early.

Summary

Whiplash injuries are becoming more common and early recognition of the whiplash syndrome is urged. The anatomic peculiarities and pathologic factors are discussed and are shown to be closely related to the clinical course. A rationale of early proper treatment is urged to obviate the longdrawn out course of a poorly treated "trivial" injury.

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PANEL DISCUSSION—DISEASES OF LYMPH NODES: THERAPEUTIC PROBLEMS

The Structure and Function of Lymph Nodes*

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This is an interesting review of what is known about lymph nodes, especially in regard to their physiologic function and the disturbances which may accompany disease.

I KNOW of no more perplexing problem in medicine today than the over-all function of lymph nodes, and in particular that of lymphocytes. In fact the whole lymphatic system seems to divide biologists into optimists and pessimists. The latter view was championed by the Clarks[1] who maintained that the lymphatic system was a vestigial structure that served no useful function in man. The other more optimistic view has been championed by Drinker, Yoffey[2] and others.[6, 7] I believe that most of my discussion today will let you know that I am inclined to this latter view.

Lymphatics first appear in annelids or round worms, reach their maximum development with lymph hearts in amphibia but persist in higher orders. Embryologically they appear at about the same time as, or possibly before the blood capillaries. In inflammatory reactions and in wound healing such as that following section or attempts at extirpation, lymphatics invariably regenerate and usually do so before blood capillaries do.[8]

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The Lymphatic System and Its Functions

The structure of the lymph nodes is given in detail in textbooks of anatomy and histology. However, none of the textbooks of physiology that I know of adequately cover the function of lymph nodes, for the function of a lymph node is inextricably tied up with the fate and function of lymphocytes. So long as the latter remain obscure the former must remain a matter of conjecture. There is convincing evidence that lymphocytes remain in circulation less than 12 hours and that the total amount of lymphocytes in circulation in the average 70 kilogram human is about 4 grams. I would roughly estimate the total size of the composite lymphatic organ as one third to one half the size of the liver. Using the more conservative figure I would guess that the total size of the lymphatic organ in man is about 600 grams and that this is composed of 50 per cent stroma, 25 per cent reticulo-endothelium and 25 per cent lymphocytes. Thus we have about 150 grams of lymphatic tissue donating about 10 grams of lymphocytes per day to the blood stream, and the level of both donor and recipient remaining constant without knowing what happened

to the donation or what it was used for. No wonder we are confused.

One's over-all views of the lymphatic system cannot help but be influenced by two basic considerations:

1. The first of these pertains to capillary permeability. I believe that there is an overwhelming body of evidence at the present time to indicate that both blood capillary endothelium and lymphatic endothelium are permeable in some degree to molecules which by present methods are classified as proteins. This does not invalidate the Starling hypothesis but merely gives a more dynamic view to that hypothesis.

2. The second point pertains to the basic concept of metabolism in a multicellular organism. This point is brought into sharp focus by the question, does every cell in the body have the capacity to fabricate all of its essential constituents from the simplest of building stones, namely amino acids, or is it not more probable that certain specialized groups of cells such as the liver, islets of Langerhans, and thyroid, have the capacity to form polypeptides and even proteins for utilization by distant groups of cells? I believe that the whole process of evolution has been dependent upon some degree of specialization and that molecules beyond the dimensions of polypeptides are fabricated in different regions of the body for incorporation into the structure of different cells and tissues far removed from the site of fabrication.

A little reflection will connect these concepts with the over-all structure and function of lymph nodes. For example, insulin definitely enhances carbohydrate metabolism not only in the liver, but in the muscles and elsewhere. Since the lymphatic endothelium offers far less of a barrier to the passage of colloidal and particulate matter than does blood vascular endothelium, we have reason to believe that insulin and other hormones probably reach the blood stream by way of lymphatic channels and that they are to some extent capable of passing not only lymphatic endothelium but also blood capillary endothelium and even cell membranes. This constitutes the modus operandi of the give and take between various organs and tissues of the body at the level of protein exchange.

The generally accepted functions of the lymphatic system can be stated quite simply:

1. Mesenteric lymphatics participate in fat absorption.

2. Lymphocytes are added to the blood stream by way of the lymph.

3. Lymph nodes act as filters.

4. Particles of colloidal size or greater are returned to the blood vascular system by way of lymphatic channels.

5. The lymphatic channels may serve as avenues for the spread of tumors, infections and metabolic disorders.

6. Antibodies are formed in part by lymph nodes.

Studies of Lymphatic System

In the following paragraphs I shall describe briefly some of my meager contacts with the lymphatic system. The most satisfactory way of studying this system is through the use of injection technics. A method whereby lymphatic endothelium could be definitely separated from blood vascular endothelium in histologic sections would be a real contribution. Until such a method has been devised our most dependable data will continue to come from injection studies. Many dyes have been employed for this purpose but one refinement of technic is not generally appreciated, namely the use of homologous serum instead of saline as the dilutent for the dye.[3-5] When a dye such as Evans blue or pontamine blue is dissolved in saline the tissue becoms blurred and the outlines of the lymphatics soon become lost. When, however, the same dye is dissolved in homologous serum the outlines of the lymphatics and lymph nodes remain sharply defined for several hours. Most of these dyes are innocuous and it is a simple matter to prepare sterile solutions of dyes using the patients own serum; in fact the solubility of the dyes is sometimes improved by this solvent.

Figure 1 illustrates the basic dynamics of the lymphatic system in diagramatic form. Under the influence of motion or massage the excess of blood capillary filtrate, that is, the portion not reabsorbed by blood capillary endothelium, diffuses through tissue spaces and enters lymphatic channels. It is obvious that during this bathing of individual cells, metabolites can be subtracted from this fluid and catabolites added to it. This constitutes the mechanism whereby building units be-

FIG. 1

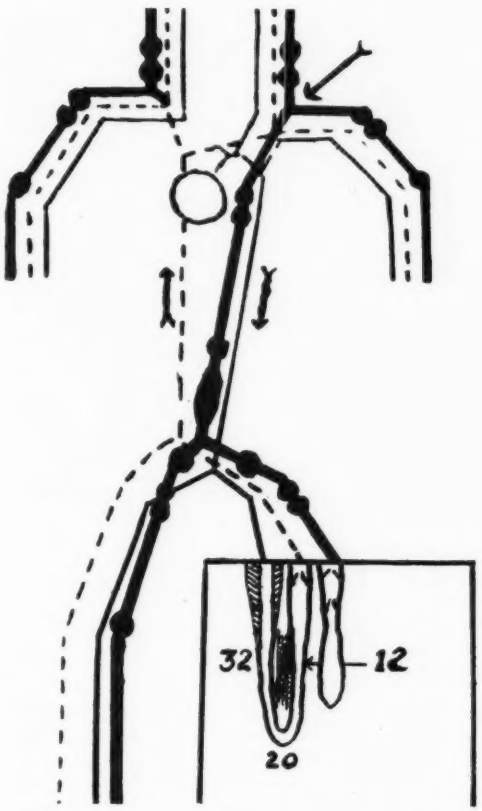


Diagram showing relationship of the lymphatic and cardiovascular systems. Heavy solid lines and balls (lymph nodes): lymphatic system. Faint solid lines: arterial system. Faint dotted lines: venous system. The insert depicts the relations of an arteriole, capillary and venule to a skeletal muscle fiber, interstitial space and a lymphatic. The figures represent millimeters of mercury in accord with the Starling hypothesis.

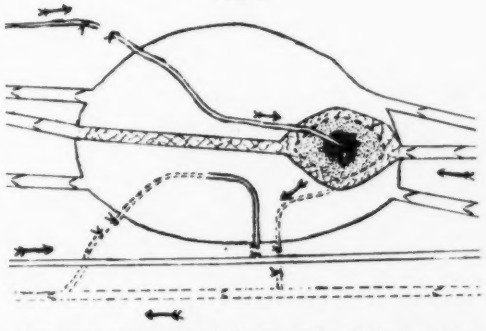
yond polypeptides formed in one part of the body could be utilized in another part of the body. Once this fluid has entered the endothelial lined channels of the lymphatic system it becomes lymph in the true sense of the word. Further alteration of this fluid takes place during this passage through lymph nodes. Figure 2 illustrates diagramatically the methods whereby alteration in this fluid takes place. The reticulo-endothelial baffle through which this fluid trickles is an extraordinarily effective device capable of filtering out bacteria and other particulate matter almost completely.[2]

At this time I wish to stress the separate identity of reticulo-endothelial and lymphatic tissue. I believe that the former is as different from the latter as the sinusoidal endothelium of the liver is from the hepatic epithelium. All pathologists are familiar with the numerous examples of dissociation of these two tissues. There may be reticulo-endothelial hyperplasia and atrophy of lymphatic tissue, hyperplasia of lymphatic tissue and quiescent reticulo-endothelium, concurrent atrophy or hyperplasia of both tissues; or even fat replacement and/or fibrosis involving both tissues.

The most obvious change in lymph during its passage through a lymph node is the addition of lymphocytes. It is impossible to state that some lymphocytes do not enter the blood stream directly, but any such direct entry into the blood stream merely adds to the problem for over two times the total number of lymphocytes in the circulation are poured into the blood stream each day by way of the thoracic duct alone.[2] Along with these lymphocytes are variable numbers (roughly 10 per cent of the total) of monocytes derived from the reticulo-endothelium.

One of the mysteries connected with lymph nodes pertains to the mechanism by which lymphocytes can pass through the reticulo-endothelial baffle of successive lymph nodes. This baffle will filter out enormous numbers of red cells, bacteria, calcite, carbon, and other formed particles of minute size[2] and yet allow lymphocytes to trickle through uninterrupted. The mechanism by which the lymphocyte hal-

FIG. 2



Diagramatic presentation of the lymphatic and blood vascular connections of a peripheral lymph node. Three afferent lymph channels enter one end of node and three efferent channels emerge from the other end. The central afferent channel breaks up into the reticulo-endothelial baffle that surrounds the germinal follicle. Lymphocytes as well as monocytes are added to the blood via the thoracic and cervical ducts. The diagram depicts severance of all blood vascular connections, a procedure that does not seriously interfere with normal vitality of the node (4).

loos "open sesame" is of fundamental interest. For example, the distinction between lymphosarcoma and lymphatic leukemia might be put on a rational basis if we could explain this "open sesame" or absence thereof.

When we come to a discussion of what happens to lymph during its passage through the lymph node we encounter certain obvious difficulties. In the first place the lymph from a single afferent trunk while having access to the entire node in reality chooses paths of least resistance (Fig. 3). Even with lymph flowing freely through a node under considerable pressure, some of the channels in the node were not outlined as can be seen in figure 4 in which thorotrast is being perfused through an afferent lymphatic channel of a popliteal lymph node of a dog. This failure to completely bathe portions of the lymph node probably accounts for the infection which was invariably encountered in the perfusion experiment to be described. We have reason to believe, certainly from these studies of popliteal lymph nodes in dogs, that bacteria are constantly being filtered out by lymph nodes. The changes within the inguinal nodes of man (both anatomic and cultural) lend support to this statement.

The second difficulty is that the perfusion

FIG. 3

X-ray picture of a popliteal lymph node of a dog being perfused with thorotrast via a cannula in an afferent lymphatic channel. This picture was taken after 0.1 ml. of thorotrast had been injected into the node and shows reticulo-endothelial baffle outlined by this procedure.

FIG. 4

The same lymph node shown in figure 3 with thorotrast flowing freely through the node. It can be seen that all of the node is not evenly filled by this procedure.

method does not separate reticulo-endothelial from lymphatic tissue. Two other impressive features of lymphatic channels are worthy of mention.

1. Valves in lymphatic channels are much more numerous than those in veins. These valves are surprisingly competent and I believe that they play an important role in the dynamics of lymph flow.

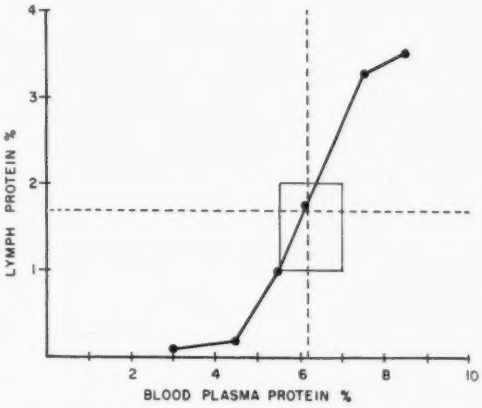
2. Each lymphatic channel is capable of carrying many many times the amount of lymph that it normally transports, for it is possible to perfuse several hundred ml. of fluid through a lymph node via a cannula in a single afferent lymphatic channel in less than an hour and at pressures that will not disrupt the normal architecture of the node in any way.

The amount of lymph that flows through a single lymphatic channel of a 10 kilo dog is roughly 1 cc. per hour for adult and old dogs and roughly twice this amount for growing puppies.[3] The concentration of protein in the lymph was the same in both young and old. Thus there is evidence of increased lymph flow during growth and development but no evidence of a decreased capillary permeability even in advanced age.

It is easy to demonstrate that lymph protein is derived in large part from blood plasma

protein and that the concentration of protein in the lymph varies with that in the blood plasma. When homologous serum in a collodion bag is placed on a rocking dialysis with an aqueous solution of a dye such as erythrosin practically all of the dye will be taken up by the serum within 12 hours, indicating a strong affinity and union between dye and serum. When this dye labeled serum is injected intravenously in an unanesthetized dog with a cannula in one the subcutaneous lymphatics, the dye labeled serum protein appears in the lymph in the cannula within a matter of minutes. Additional evidence is shown in figure 5 in which the lymph proteins were compared with those in the blood plasma when the latter was studied under normal, hypoproteinemic, and hyperproteinemic conditions. There is also evidence from this type of experiment for a critical zone of protein filtration. This is seen in figure 6.

FIG. 6

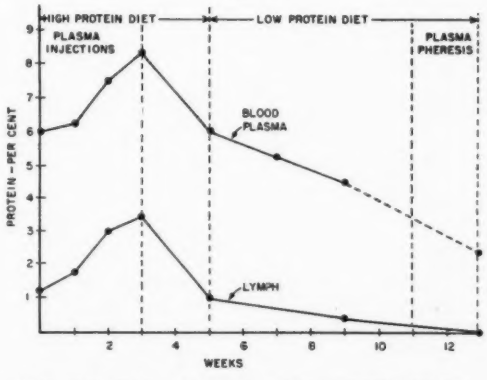


Lymph protein concentration plotted as a function of blood plasma protein concentration (from the data in figure 5). The faint cross lines in the center represent the average "norm." The rectangle covers over 95 per cent or "normal" figures. The graph presents evidence for a critical zone of protein filtration.

Chemical Studies

When popliteal lymph nodes of dogs are perfused with artificial lymph (1 part serum and 1-4 parts Tyrode's solution with and without added glucose) through a single afferent lymphatic channel and the perfusate is collected under aseptic conditions, it is possible to carry out chemical analyses on afferent and efferent "lymph," and to deduce from the analysis some of the functions that might occur *in vivo*. The chemical determination which we have used most extensively is that for reducing substance which is interpreted as glucose. The influence of temperature on glucose consumption is shown in figure 7. The oxygen quotient greater than 2 is usually interpreted as evidence for an enzymatic activity.

FIG. 5



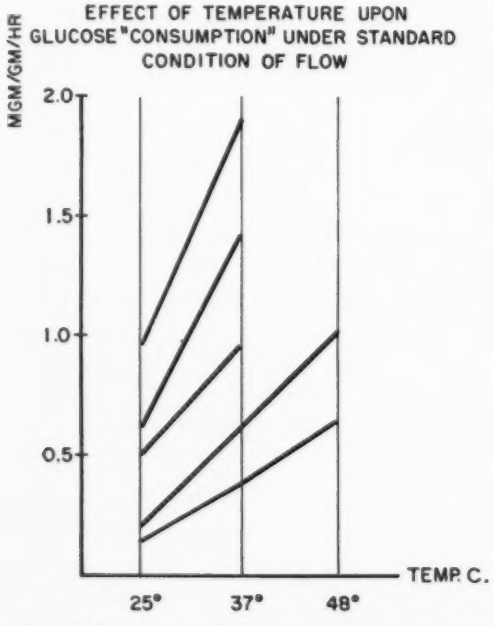
The relationship of lymph protein concentration (subcutaneous lymph from foot of dog) to that of blood plasma under varying experimental conditions. A high protein diet was fed during the first five weeks of the experiment. This was supplemented by repeated injections of donor's plasma protein during the first three weeks. From the fifth to thirteenth week the dog was fed a low protein diet, supplemented with repeated plasmapheresis during the last two weeks. There is striking correlation between the concentration of blood plasma protein and that in the lymph.

The relationship between pressure and glucose consumption is shown in figure 8. In general it is a straight line function but with increased flow related to increased pressure the limits of error for the method of glucose determination become the limiting factor. Thus we had to stabilize on an "optimum" flow under standard conditions. When this was done there was a sharp drop in reducing substance during passage through the node and this could be accounted for in large part by a corresponding fall in bound CO_2 and in CO_2 combining power.[4] This indicates that anaerobic glycolysis is the method whereby glucose is consumed. No attempt was made to exclude oxygen from the system but even under these conditions the chemical data indicate that the major mechanism for glycolysis is anaerobic. No such drop in reducing substance was demonstrated when the thyroid gland was perfused through an artery!

I believe that this evidence for anaerobic glycolysis by lymph nodes is a potentially important finding. Our problem basically is to

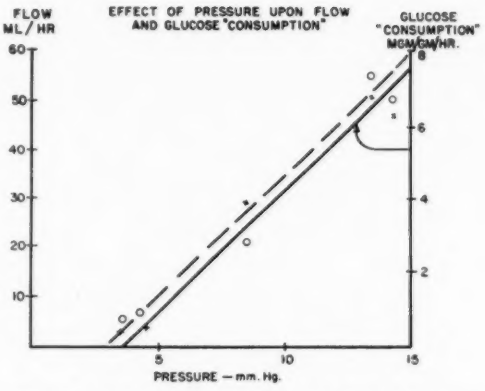
define the function and fate of the lymphocyte. Until this is done our morphologic data will have little coherent meaning. I have lived with this concept of potential anaerobic glycolysis for over a decade and I find that it enhances my interest greatly as I study routine histopathologic material and see collections of lymphocytes in chronic inflammatory reactions, about the advancing margins of neoplastic processes and curious collections of lymphocytes in locations where infections are not generally suspected, such as the lymphorrhages of myasthenia gravis, the focal accumulation of lymphocytes in the adrenal cortex, the massive collections of lymphocytes (some with germinal centers) in the thyroid in Hashimoto's struma and the general activation of lymphatic tissues in cases of poliomyelitis and hyperthyroidism. I have yet to see a lymphocyte in one of these locations in which I cannot imagine that it is not answering some call for help, and that it is trying to meet this call for help by furnishing energy in the form of anaerobic glycolysis. Of course I like to believe that this energy is directed

FIG. 7



The influence of temperature upon the "glucose consumption" of a popliteal lymph node of a dog perfused with artificial lymph *in vitro* under standard conditions of lymph flow. Glucose consumption is expressed in mg. per Gm. of lymph node per hour.

FIG. 8



The effect of pressure upon flow (broken line) and glucose consumption (solid line) of a dog popliteal lymph node perfused with artificial lymph *in vitro*. Glucose consumption is expressed in mg. per hour per Gm. of lymph node. The temperature in these experiments was 37° C.

along constructive lines but this is becoming teleological.

There is another mid-zonal group of cases in which an infectious agent is commonly suspected but not always demonstrable,—chronic pericholangitis, chronic cholecystitis, and chronic pyelonephritis,—to mention only three such examples. It does not benefit patients to state that the lymphocyte characterizes chronic inflammation without an attempt to state how it does this. It does not help patients to state that the lymphocytes around the advancing margins of a cancer are protective when this finding is not too consistent with the known propensity of carcinoma to metastasize to lymph nodes. We must come to some concept of the function of a lymphocyte and explore the possibilities thereof. Time and experience will let us know whether or not the hypothesis benefits patients.

I realize that this presentation is provocative and I do not wish to turn it into a polemic.

Summary

I will summarize by stating that phylogenetically, ontogenetically, physiologically and pathologically I know of no data pertaining to the lymphocyte that are inconsistent with the hypothesis that one of its major functions is to serve as a potential reservoir for anaerobic glycolysis. I wish that you would keep this suggested function before you.

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The Peripheral Blood and Bone Marrow Cells in Diseases of the Lymph Nodes*

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The author emphasizes the variability which may be encountered in the smears of the peripheral blood and the bone marrow in diseases of the lymph nodes. Nevertheless, these laboratory studies, when correlated with the clinical picture, may be most helpful in diagnosis.

THE DIAGNOSIS of disease characterized by enlargement of the lymph nodes is often difficult and challenges the acumen of specialists in various fields. A study of the peripheral blood may, in conditions such as leukemia and infectious mononucleosis, establish the diagnosis. In the majority of diseases of the lymph nodes the peripheral blood and bone marrow changes are not specific, but taken together with the history and physical examination furnish information which is of great worth. Hematologic findings are also of help in the interpretation of lymph node biopsies.

General

Hematologists or pathologists examining peripheral blood smears, bone marrow or lymph node biopsy material should have full information about the clinical picture, the results of previous laboratory examinations and treatments used, including exact dates in relation to the time the specimen was obtained, so that the patient can derive maximal benefit from the consultation. Many physicians labor under the delusion that tissue changes are always specific and that the pathologist's judgment would be impaired if all of the facts were known to him. The interpretation of tissue changes without background knowledge reduces the consultant to the role of a technician who is often forced to give a descriptive diagnosis, rather than a medical opinion. Often the consultant cannot make a definitive diagnosis, but he can, on the basis of combined facts, rule out certain possibilities and make valuable recommendations.

The blood picture in diseases of the lymph nodes is not static. There may be marked differences in the counts and in the distribution of cells within relatively short periods. Often the diagnosis may not be obvious at the time of the first examination, but becomes obvious when the trend in one direction or the other is established.

The study of blood smears from patients with lymphomatous diseases should not be routed through the routine hospital or clinic

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channels along with admission and screening blood tests, for the average technologist, regardless of how well trained or conscientious, is likely to miss the occasional "blast" or malignant cell, or abnormalities in nuclear structure when specimens are hurriedly examined. It is well known that the majority of technologists who carry the load of work in most hospitals have not been well trained as cytologists and often neglect the fundamentals in the technic of making and examining smears.

Smears are often too thick. The leukocytes "round up" in the process of drying, thus obliterating nuclear chromatin structures and cytoplasmic details. Smears may be too thin or made in such a manner that the larger cells, which tend to be shoved toward the sides, are pushed over the edge or are so close to the edge that they cannot be counted when a mechanical stage is used. Counting of cells in the middle of the smear only and ignoring the margins and ends often leads to an increase in lymphocyte percentages suggestive of lymphocytic leukemia. Differential counts made by traversing the margins of the film and ignoring the center of the smear may give an erroneous increase in neutrophils and monocytes and fail to detect a significant lymphocytosis.

Peripheral Blood

Neutrophils. A normal white cell count with an essentially normal differential count in the presence of lymphadenopathy is suggestive of a relatively benign type of lymphoma, such as giant follicular lymphoblastoma or the very early stages of Hodgkin's diesase or sarcoma before the development of degenerative changes or metastases. Normal leukocyte counts may also be found in sarcoid or in lesions in which there is fibrosis and calcification.

A leukocytosis within the range of 10,000 to 20,000 per cu. mm. with a predominance of neutrophils and an absolute lymphopenia suggests a pyogenic infection, fungus disease or metastatic tumor. The presence of an increased number of eosinophils, monocytes, lymphocytes and occasional plasmocytes together with neutrophils suggests a chronic inflammatory lesion or allergic condition.

A decreased white cell count associated with neutropenia and a relative lymphocytosis makes one think of viral disease, nonpyogenic infections, such as tuberculosis and undulant fever, and leukemia in the aleukemic phase.

In Hodgkin's disease there may be a normal number of neutrophils or a slight increase in neutrophils with an absolute decrease in lymphocytes. This unusual combination of leukopenia and lymphopenia without neutropenia is rarely observed in conditions other than Hodgkin's disease. A relative increase in monocytes and a normal or slightly increased eosinophil count are other common findings in Hodgkin's disease.

In rare situations there may be a leukemoid reaction of the myelocytic type with total white cell counts above 50,000 per cu. mm. in Hodgkin's disease and other types of lymphoma. In some cases there may be a significant increase in eosinophils. The differential diagnosis between true myelocytic leukemia and variant forms of myeloproliferative disease and lymphomas with a leukemoid reaction may be extremely difficult even if all types of study including lymph node and bone marrow biopsies are utilized.

Eosinophils. These are most frequently increased in chronic infections, in allergic states, in myelocytic leukemia and in Hodgkin's disease. As a rule, eosinophils are decreased in acute pyogenic infections, tuberculosis and in monocytic and lymphocytic leukemias.

Basophils. An increase in basophils in the presence of lymph node enlargement occurs in myelocytic leukemia and in practically no other condition. There may be a marked increase in basophils in chronic myelocytic leukemia before the patient becomes incapacitated or before there is manifest enlargement of lymph nodes or spleen.

Lymphocytes. An absolute increase in lymphocytes means hyperplasia of lymphatic structures with delivery of these cells into the blood stream faster than they are destroyed. An absolute increase in lymphocytes in children is frequently observed in chronic infectious diseases and in allergic states and usually does not mean leukemia, but in an adult with a total count above 20,000 per cu. mm. with 60 per cent or more lymphocytes, the most likely diagnosis is chronic lymphocytic leukemia. The diagnosis is strengthened if the patient appears to be

in good health. In most other conditions in which there is significant leukocytosis the patient has constitutional symptoms. Often patients with chronic lymphocytic leukemia have high counts without enlargement of the lymph nodes or spleen. The authors have never seen a patient with lymphadenopathy and splenomegaly due to lymphocytic leukemia who had at the same time a normal blood picture. In the early stages of chronic lymphocytic leukemia the lymphocytes are small and mature. Smudges are increased. Lymphoblasts and nucleated red cells are rarely seen. The thrombocytes are normal, and there may be normal or even increased erythrocyte values. As the disease progresses, the number of lymphocytes increases, more immature cells appear and anemia and thrombocytopenia develop.

In acute lymphocytic leukemias the initial counts may be decreased but, as a rule, the total white cell count is elevated. There are numerous immature cells and typical lymphoblasts, characterized by round, reddish nuclei with fine chromatin structure and well-defined nucleoli and with narrow rims of bluish nongranular cytoplasm. Nucleated red cells are usually demonstrable. Anemia of the normocytic normochromic type and thrombocytopenia are usually demonstrable at the time the patient is first seen.

One of the morphologic variants of the lymphocyte, which is indicative of abnormal lymphocytic proliferation, is the cell with a well-defined cleft as seen from the side, or a "crack" or cleavage line as seen from above. These cells, called "hematogones" by Rosenthal and associates[1] are probably cells which have abnormal chromatin structure and have undergone partial division in the process of abnormal mitosis. Lymphocytes with nuclear clefts are usually small and have narrow rims of cytoplasm. The chromatin pattern is coarse and there are no nucleoli. Cells of this type may be found in giant follicular lymphoblastoma and may be the only abnormality detectable in the blood in this condition. They are also frequently found in lymphocytic leukemias. Cells with deep clefts may be found occasionally in miscellaneous conditions, hence they cannot be interpreted as reliable signs of lymphocytic proliferation of a malignant type.

Infectious mononucleosis is characterized by a variable white cell count. There is usually a moderate leukocytosis at the time the lymph nodes are enlarged and the patient seeks medical aid. Infectious mononucleosis, in contrast to leukemia, presents a pleomorphic cellular picture in which many types of cells are found. The predominant cells are lymphocytes which often constitute 60 per cent or more of the differential count. Many of the lymphocytes are large, with scalloped margins and unevenly stained bluish cytoplasm. Some may have vacuoles in the nucleus, a foamy cytoplasm and prominent azurophilic granules. The monocytes are increased. The most diagnostic feature is the presence of atypical cells which cannot be identified readily, but which have characteristics intermediate between large lymphocytes, monocytes and plasmocytes. Blast-like cells may be present. Nucleated red cells are rare. Basophils are demonstrable. A slight increase in eosinophils is the rule. Neutrophils with a slight left shift usually comprise 10 to 20 per cent of the cells. The blood picture together with the clinical course is usually diagnostic. Heterophil antibody studies are of confirmatory value. Negative heterophil agglutination test does not rule out the disease.

In infectious diseases of childhood, other than infectious mononucleosis, such as acute infectious lymphocytosis, German measles, pertussis, tuberculosis and virus infections there is often a hyperplasia of lymphatic tissue and a significant increase in lymphocytes in the peripheral blood. Correlation of the blood picture with the clinical findings and watchful waiting with repetition of the hematologic studies is often sufficient to make the diagnosis in these cases, without resorting to bone marrow examination or lymph node biopsy.

Monocytes. Enlargement of lymph nodes is rarely a presenting sign in monocytic leukemia. As a rule, the peripheral blood picture and bone marrow examination furnish adequate information upon which to make a diagnosis. Typical "blasts" and other immature and pathologic cells, together with large cells having folded nuclei, pseudopods, vacuoles and phagocytized particles are found. As a rule, there is an associated anemia and thrombocytopenia. Nucleated red cells are usually demonstrable.

Monocytes are increased in chronic pyogenic

infections, in nonpyogenic infections and viral diseases, in sarcoid and in Hodgkin's disease.

Erythrocytes. In the various lymphomas there is little or no anemia in the early stages of the disease with exception of acute leukemias. In all lymph node diseases, including Hodgkin's disease, lymphosarcoma, and leukemia there is anemia as the disease becomes more widespread and develops metastases to tissues other than lymph nodes. It has been shown that the anemia is not due entirely, as was formerly thought, to the crowding out of normal cells by malignant cells, but to alteration in the structure of erythrocytes causing them to have a shortened survival in the circulation. The bone marrow, as a rule, is hyperactive but in spite of compensatory blood cell formation is unable to form cells as fast as they are destroyed. A rapidly progressive anemia is a poor prognostic sign. The anemia often improves when the disease is treated, and is not *per se* a contraindication to treatment. On the other hand, irradiation may injure cells and later play a role in anemia. Lymphomas often are associated with anemias of the hemolytic type. In these cases the Coombs test may be positive and beneficial effects may be obtained by steroid threapy and splenectomy.

Thrombocytes. These are rarely decreased in chronic lymphocytic leukemia in the early stages of the disease, but are significantly decreased in the later stages. In the acute and subacute lymphocytic leukemias and in monocytic leukemia there is usually thrombocytopenia at the time the patient is first seen by the physician. Hemorrhagic phenomena, petechiae and thrombocytopenia may, in rare cases, be associated with the terminal phases of any of the malignant lymphomas, but are the exception rather than the rule.

Bone Marrow

In conditions characterized by enlargement of the lymph nodes in which the diagnosis is not obvious from the history, physical examination, initial laboratory tests and radiologic studies, lymph node biopsy and/or bone marrow examination are indicated. Lymph node biopsy is recommended as an initial procedure in those instances in which there is an enlargement of a single node or a unilateral group of nodes and in those conditions in which no abnormality is demonstrable in the peripheral blood picture. The examination of the bone marrow should precede the lymph node biopsy in those instances in which there is generalized lymphadenopathy, or in conditions in which there are definite cellular abnormalities in the peripheral blood. A study of the bone marrow is particularly indicated in diseases associated with leukopenia, refractory and nonregenerative anemia and thrombocytopenia.

It is superfluous to examine the bone marrow of patients who have diagnostic cells in large numbers in their peripheral blood.

On the other hand, if there is any doubt concerning the diagnosis, or if the patient is referred for consultation, indicating that there has been a doubt in the referring physician's mind or in the minds of the patient and family, the bone marrow examination should be performed. There is no contraindication to the procedure except the slight discomfort and cost.

In patients with known leukemia who have received radiation therapy or cytotoxic drugs and who have reached a refractory state or have developed anemia or thrombocytopenia, the examination of the bone marrow will help in guiding further treatment. If the marrow is relatively acellular and replaced by fibrous tissue, further treatment other than symptomatic and supportive measures are contraindicated. On the other hand, if the marrow is replaced by leukemic cells, further treatment may be cautiously tried.

In diseases characterized by fever or in which there is suspicion of an infectious process, cultures of the material aspirated from the marrow are indicated. Culture media for fungi, tubercle bacilli and for miscellaneous organisms should be inoculated.

In the interpretation of the marrow differential, it is imperative that peripheral blood smears be available for examination at the same time, for admixture of peripheral blood cells with the material aspirated from the marrow may give an entirely erroneous interpretation. For example, one may have a patient with 70 per cent lymphocytes in the peripheral blood. Due to faulty technic in aspiration, the material obtained may contain little or no marrow but consist mostly of peripheral blood. A differential marrow count

of 60 per cent lymphocytes in a representative marrow would be practically diagnostic of lymphocytic leukemia, but a 60 per cent count in a diluted marrow with a peripheral blood count of 70 per cent would have no interpretative value. On the other hand, if a patient had 70 per cent cells in the peripheral blood and 96 per cent in the bone marrow it would be significant.

Tissue sections as well as smears of bone marrow should be available for study. Thin smears stained with Wright's stain make it possible to identify individual cells and to study details of nuclear and cytoplasmic structure, but give unreliable information concerning the degree of cellularity, the degree of dilution with peripheral blood and the anatomic pattern. Tissue sections may reveal fibrosis, degenerative changes, granuloma or malignant cells not detectable in the examination of the smears. If bone marrow is collected by needle aspiration technics, sections should be made of the residual clot. If surgical biopsy is performed, the surgeon should aspirate bone marrow using a standard marrow needle and a syringe after the periosteum has been exposed and before the biopsy is taken. Smears made from material aspirated from an open wound is likely to contain peripheral blood only and few marrow cells. If it is not possible to obtain marrow by aspiration at the time of surgery, imprint or "dab" preparation of tissue should be made by pressing a slide down on bits of marrow tissue and lifting the slide straight up. A thin layer of cells sticks to the glass giving excellent cell detail and maintaining somewhat the anatomic pattern. The tissue should never be swished back and forth across the surface of the slide, for this tears and distorts the cells.

The smears of the bone marrow and the tissue section should be interpreted together and one report submitted. Separate examinations by the hematologist, who examined the patient and the smear, and the pathologist, who examined the fixed tissue, may be necessary in order to maintain training programs, but each person on the team should have the advantage of the total picture.

In the diagnosis of diseases of the lymph nodes, the bone marrow examination is most useful in establishing the diagnosis of leukemia or excluding leukemia. In the early stages of leukemia, before there is lymph node enlargement and splenomegaly, clinical symptoms or anemia, there may be a significant leukocytosis and absolute increase of lymphocytes in the peripheral blood without a significant increase in lymphocytes in the bone marrow. Thus, the bone marrow examination is not necessarily diagnostic of lymphocytic leukemia in the early stages. By the time the lymph nodes have become readily palpable and visibly enlarged there is usually an increase in lymphocytes above 30 per cent. The greater the degree of replacement of the normal marrow cells by lymphocytes the more diagnostic does the marrow examination become, but one cannot be dogmatic and fix an exact level above which leukemia is present and below which leukemia is absent. As elsewhere in medicine the diagnosis is based on combined facts.

The bone marrow is frequently involved in Hodgkin's disease but the diagnosis of this disease by bone marrow smears alone or by smears plus tissue sections is seldom possible. On the other hand, the bone marrow findings are helpful as adjunctive evidence in making the diagnosis or excluding the disease. The marrow is usually quite cellular with an essentially normal ratio of major cell types to each other. There is, as a rule, a slight maturation arrest of the myelocytic and erythrocytic cells. Megakaryocytes are present in normal numbers. The eosinophils, plasmocytes, and monocytes tend to be slightly increased. The lymphocyte count is variable but within normal limits. Undifferentiated mesenchymal cells, granular histiocytes (Ferrata cells) and atypical macrogranulocytes are slightly increased. Occasionally one may find large monocytoid cells with large, folded and multilobulated nuclei which correspond to the cell known as the Reed-Sternberg cell. These cells, while suspicious, are found in so many other conditions that a diagnosis based on their presence is not warranted. Others claim to have the ability to identify Reed-Sternberg cells but the authors have not been initiated in this esoteric fraternity.

Occasionally granulomatous lesions with characteristic and diagnostic cell structures may be found in biopsies of marrow. As a rule, the granulomatous lesions are not specific.

The bone marrow examination and peripheral blood examination rarely may reveal

malignant cells which are confirmatory in the diagnosis of sarcoma. As a class, malignant cells are large, have large and usually round nuclei, early nuclear chromatin structures and a bluish cytoplasm. In bone marrow smears and tissue sections they usually take a deeper stain than do the surrounding normal cells. They tend to occur in groups or in syncytical masses. They do not have the morphology of normal marrow cells and therefore are interpreted as cells which are foreign to the bone marrow. Tissue sections are of value in the identification of the type of metastatic cell, for few cytologists can identify the type of malignancy by the structure of individual cells alone.

Summary

In the interpretation of smears and biopsies, the pathologist needs complete information in order to give the patient maximal benefit.

The blood picture in lymphomatous diseases is not static. Diagnoses which are not evident at the time of the first examination may be established by following the progress of cellular changes. Important cytologic details may be missed if the smears are examined in a routine manner. Errors may be due to improper training of staff, inadequate time and to improper technics.

Neutrophilia suggests pyogenic infection, fungus disease or metastatic malignancy. Neutrophilia accompanied by slight increase in eosinophils, lymphocytes, monocytes and plasmocytes suggests chronic infection and allergic states. Neutropenia suggests viral disease, nonpyogenic infection and aleukemic leukemia.

The blood and bone marrow picture in Hodgkin's disease is variable and is not diagnostic. The most characteristic peripheral blood combination is a normal total white cell count with a lymphopenia without neutropenia, associated with a slight increase in monocytes and eosinophils. Large, monocytoid and multilobulated cells of the Reed-Sternberg type are sometimes demonstrable in marrow smears but similar cells are found in other conditions.

An absolute increase in lymphocytes in the peripheral blood is indicative of a proliferative lymphocytic process. Lymphocytosis is common in children and is usually not due to leukemia. An absolute and sustained lymphocyte count in an adult is most likely due to chronic lymphocytic leukemia. Small lymphocytes with clefts and well-defined cleavage lines are frequently demonstrable in lymphocytic leukemia and in giant follicular lymphoblastoma but are not specific for malignancies of the lymphatic system.

In infectious mononucleosis there is a pleomorphic cellular picture with an increase in lymphocytes, monocytes and eosinophils and atypical cells of the lymphocytic-monocytic and plasmocytic types.

Monocytic leukemia is characterized by immature cells of the monocytic series in peripheral blood and bone marrow, associated with anemia and thrombocytopenia.

In acute leukemias and in the later stages of chronic leukemia there is progressive anemia and thrombocytopenia. In other malignancies of the lymph nodes anemia develops later and thrombocytopenic purpura is rare.

The bone marrow should be examined previous to lymph node biopsy in conditions in which there is generalized lymph node enlargement and abnormal cells in the peripheral blood. Lymph node biopsy should be performed first when there is enlargement of a single node or a unilateral group and in conditions with a normal blood picture.

The bone marrow is not needed for diagnosis in leukemias with marked leukocytosis. The chief indication for marrow examination is pancytopenia.

Cultures of bone marrow are indicated in patients with unexplained fever. The peripheral blood and the tissue sections should be examined at the time the marrow smears are examined.

The bone marrow examination is most useful in the diagnosis and differential diagnosis of the leukemias. In rare instances it may be diagnostic in sarcoma, Hodgkin's disease and infection.

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Discussion (Abstract)

Dr. Lauren V. Ackerman, St. Louis, Mo. It is unfortunate for the pathologist who has to look at lymph nodes that varied pathologic processes give similar morphologic patterns, and so after one has formed a certain mental impression, as that a picture pretty

well fits tularemia, one discovers there are several other things that also look like tularemia.

It is important, in all these diseases, to take into consideration the total picture. I feel, also, that it is very important that one culture lymph nodes. We urge this in repeated discussions with surgeons and internists. We discovered that many surgeons do not talk to internists and vice versa. We are in favor of their talking to each other, and also occasionally in talking to the pathologist. In that way one can get the greatest number of accurate diagnoses.

We take half of the lymph node and put it away in a sterile Petri dish in a deep-freeze and, if microscopically, we cannot make a diagnosis we sometimes use that to help us. The pattern of the lymph node may direct us into the right direction.

Dr. Russell L. Holman, New Orleans, La. In answer to the specific qusetions,—lymph will clot, lymph does contain platelets. I do not believe that the fibrinogen in lymph is anywhere near as great as it is in the blood system nor is the number of platelets in lymph as great as it is in circulation. I think that part of the differential may be related to just pressure relationships and part of it may be related to the differential in concentration of fibrinogen and platelets that you have just mentioned.

There is one phase of lymph that is not commonly appreciated. In the absence of passive motion, active motion or massage, there is practically no lymph flow. I think a portion of this lymph flow is related to mobile structures and the lethargic motion of muscles, surrounding tissue, and of course we also have diaphragm and cardiac muscle. I believe that the greater ease of penetration, greater permeability of the lymphatic endothelium as contrasted to that of blood capillary endothelium is related primarily to two things,—one is pressure, and the second, motion and massage, and possibly a third, one cannot exclude the importance of the differential concentration of fibrinogen and platelets.

Dr. Gretchen V. Squires, Pensacola, Fla. Dr. Holman has not mentioned a possibility of histamine release on or upon the fragmentation or death of lymphocytes as one possible agent that might affect permeability of lymphatics and some of the morphologic changes that we see.

Dr. Albert E. Casey, Birmingham, Ala. I would like to make a point on Dr. Diggs' paper. I believe he said something about the surgeon doing sternal punctures. I believe most of us do our own punctures for it saves the patient a great deal of money, and makes a difference as far as the routine examinations in the laboratory are concerned.

The use of supravital stains for differentiating monocytes in infectious mononucleosis and monocytic leukemia is helpful in routine studies.

Dr. Israel Davidsohn, Chicago, Ill. Many believe that these cells are neoplastic, the multinucleated as well as the mononuclear cells of Hodgkin's tissue. I do not share this opinion, because I fail to see that the neoplastic nature of Hodgkin's disease has been established. The question of whether these cells are specific for the disease has not been settled. Whatever the case may be, I am unwilling to diagnose Hodgkin's disease on a microscopic section until and unless I can see Reed-Sternberg cells. The situation is not unlike that in the serologic diagnosis of syphilis. The beef heart antigen of the Wassermann test has certainly no specific relation to the Treponema pallidum, but for practical reasons a positive test is accepted as indicative of syphilis. Similarly, the finding of Reed-Sternberg cells is diagnostic for Hodgkin's disease, even if the two go together in only 98 per cent of cases.

Immunohematologic Aspects of Diseases of Lymph Nodes*

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Increasing knowledge of hemoagglutination and hemolysin reactions is establishing relationship to certain diseases of the lymph nodes.

THE TITLE of this paper refers to diseases of lymph nodes associated with, or even characterized by, changes in the blood cells and plasma of immunologic nature and demonstrable with the help of hemagglutination or hemolysin tests.

According to a definition of immunohematology which I suggested sometime ago,[1] this new branch of clinical pathology encompasses the diseases of blood and blood forming tissues of which the causes, the pathogenesis or clinical manifestations have been shown to be determined by an antigen-antibody reaction, or by a phenomenon simulating such a reaction. So-called auto-immune hemolytic disease, a form of acquired hemolytic anemia, infectious mononucleosis, and hemolytic disease of the newborn (fetal erythroblastosis), obviously belong here. Recently, cases of thrombocytopenia and leukopenia have been observed in which antibodies were responsible for the disease. It is probable that further progress will add other diseases to those mentioned, if antigen-antibody reactions are shown to be involved in them.

This hybrid subdivision of hematology and immunology has its own methodology, with the usual limitations of a new discipline. It may well be that this conception of immunohematology will undergo changes, expansions or contractions, as the progress of our knowledge in this field will call for.

At the present time, we are going through the exciting period of crystallization of a relatively new science, which resulted from the union of two branches of medical science.

I intend to discuss briefly immunohematologic aspects of infectious mononucleosis, hemolytic anemia, thrombocytopenia and leukopenia.

Infectious Mononucleosis

The lesion in which immunohematology has found the most practical application is infectious mononucleosis. This statement is based on the fact that there are cases of this disease which cannot be diagnosed without serologic tests. In spite of the fact that a sensitive, highly specific and simple test has been available for almost 20 years,[2] it is frequently used improperly. It is to be regretted that reports are still being published and conclusions drawn which are not valid, only because the proper test was not done. For that reason, I chose to discuss briefly three points which have some bearing on the present status of the serologic tests for infectious mononucleosis.

Point one has to do with difficulties in the clinical diagnosis of infectious mononucleosis. They are the same today as they had been 20 and 30 years ago.

In the typical case, the diagnosis is easy. However, there are not infrequent atypical cases in which everything seems to combine to make the clinical diagnosis difficult or almost impossible. The complex diagnostic problems encountered in infectious mononucleosis have been presented in detail in a previous publication.[3]

The second point in this discussion is the diagnostic value of hematologic findings. The differential blood count is characteristic but by no means specific. Furthermore, the period during which the highly characteristic blood picture is present is relatively brief. This limits the diagnostic value of morphologic blood findings to the early stages when the disease is fully developed.

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The third point is the misconception regarding the validity of the so-called heterophilic antibody test, also called the Paul and Bunnel test. It is not generally appreciated that this test is entirely nonspecific and presumptive in character. Sheep agglutinins are present in low titers in the blood of most normal persons (usually not higher than 1:28) and in elevated titers in patients with a variety of conditions of all kinds. In the technic which I recommended, titers of 1:56 and 1:112 are borderline, titers of 1:224 or higher are frequently seen in infectious mononucleosis but may be present also in other conditions. On the other hand, titers lower than 1:224 are frequent in infectious mononucleosis.

The distribution of the low titers in our material differed, depending on the stage of the disease. In our experience, exclusive dependence on the Paul and Bunnel or heterophilic antibody test, or what we call the presumptive test, would give false negative results in about 36 per cent of late cases. Hence the conclusion that the differential test should be done regardless how low the titer of the presumptive test.

TABLE 1

THE PRESUMPTIVE TEST FOR INFECTIOUS MONONUCLEOSIS

Interpretation of Results

The finding of a titer of 224 or higher in a person who did not receive an injection of horse serum or of horse immune serum in the recent past, and who presents a clinical picture and hematologic findings suggestive of infectious mononucleosis, indicates with a high degree of probability the presence of infectious mononucleosis.

Antisheep agglutinins in titers up to 56 may be found in normal persons and in patients with a variety of diseases. Occasionally, also titers of 112 may be found in such persons.

When titers of 224 or higher occur in patients with serum disease, or following injection of horse immune serum;

When the presumptive test shows titers of 224 or higher, but the characteristic clinical or hematologic findings of infectious mononucleosis are absent;

When the test shows titers of 112 or less, but the characteristic clinical or hematologic findings of infectious mononucleosis are present;

Then the differential test for infectious mononucleosis is indicated.

The Differential Test for Infectious Mononucleosis

Principle

Antisheep agglutinins in infectious mononucleosis are NOT absorbed by guinea pig or horse kidney, they are NOT of the Forssman type.

Antisheep agglutinins in *serum disease* and in *normal persons* are readily absorbed by guinea pig and horse kidney; they are of the Forssman type.

Indications

1. *Borderline titers of 112 or less* in the presumptive test in patients with characteistic clinical or hematologic findings, or history, of infectious mononucleosis;
2. *Titers of 224 or higher* in the presumptive test in patients without characteristic clinical or hematologic findings, or history, of infectious mononucleosis;
3. *Serum disease.* This condition may mask the clinical picture of infectious mononucleosis. The titer of the presumptive test may be high in both diseases. The differential test will reveal the true nature of the antisheep agglutinins.

TABLE 2

THE DIFFERENTIAL TEST FOR INFECTIOUS MONONUCLEOSIS

Interpretation of Results

In serum of patients with infectious mononucleosis, absorption with guinea pig or horse kidney will remove some of the agglutinins for sheep red cells, but, as a rule, not less than one-fourth of the original titer will remain in the serum after absorption.

If all or almost all (more than 90 per cent) of the agglutinins have been removed in the differential test, infectious mononucleosis is excluded.

In our experience, *infectious mononucleosis is the only disease in which at least 12 per cent of the original titer of antisheep agglutinins remains after absorption with guinea pig or horse kidney.*

The Differential Test. The differential test includes treatment of the serum with a suspension of guinea pig kidney or horse kidney, potent Forssman antigens,[4] and with beef cells. The former do not remove the infectious mononucleosis antibody, the latter does. Only if both parts of the differential test give results as stated in the preceding sentence is the test serologically positive for infectious mononucleosis.

The serologic test may become positive weeks after the onset of the disease. Hence, the test should be repeated several times if the clinical manifestations suggest the disease.

The interpretation of the tests for infectious mononucleosis is summarized in tables 1 and 2.

Immunohematologic Aspects of Hemolytic Anemia

Since the introduction of the antiglobulin test (better known as the Coombs test),[5] there has been a marked increase in reports on the incidence of acquired hemolytic anemia including those in various lymphomas. The frequency of this finding has increased sufficiently to make tests for auto-antibodies essential for the diagnosis of acquired hemolytic anemia and in the study of lymphomas, such as lymphosarcoma, leukemias and Hodgkin's disease.

In our experience, the direct antiglobulin test has been more frequently positive in idiopathic than in symptomatic hemolytic anemia.

Cell bound and free auto-antibodies. In addition to cell bound auto-antibodies, which are detected with the direct Coombs test,

free auto-antibodies may also be found in the serum. They are, as a rule, warm incomplete antibodies, which means that they do not react in saline at 37° C., but only when one of the following technics is used: (1) a macromolecular diluent such as human plasma of group AB, or bovine albumin for the suspension of red cells; (2) the indirect antiglobulin (Coombs) technic; (3) enzyme treated red blood cells. In the latter technic, saline is used as diluent.

Tests for auto-antibodies. With the help of the technics just mentioned, auto-antibodies can be detected in most cases of idiopathic and in many of symptomatic acquired hemolytic anemia.

Relation of free to cell bound auto-antibodies. In most instances, cell bound and free auto-antibodies are found simultaneously. When only one is present, it is most frequently the cell bound variety, which gives the positive direct Coombs test. Rarely the opposite is true; only free auto-antibodies are found. The latter may have special significance and will be discussed later. There is no reason to assume that cell bound or fixed antibodies and free or circulating antibodies are different from each other.

Free auto-antibodies with negative direct Coombs test. Occasionally, free auto-antibodies may be present in bloods with negative direct Coombs tests. In our series of 38 patients in whom auto-antibodies were studied, five (or 13 per cent) had a negative direct Coombs test, whereas one-third of patients with a positive direct Coombs test had no detectable auto-antibodies.[6] Since the series just quoted was completed, the number of cases with a negative direct Coombs test in whom free auto-antibodies were detected has risen considerably. Increased sensitivity of tests for free auto-antibodies is responsible.

Judging from reports in the literature, tests for auto-antibodies in hemolytic anemia are frequently limited to the direct Coombs tests. Tests for free auto-antibodies are reported less frequently. The lack of interest in free antibodies is in accord with the prevalent opinion that tests for free antibodies have nothing to offer in line of diagnosis not already provided by the Coombs test. In the light of the preceding discussion, tests for free auto-antibodies may be of value in four ways.

Reduction of false negative results. In the first place, occasional, though admittedly rare cases of auto-immune hemolytic anemia may not be diagnosed serologically with the direct Coombs test alone. One could attribute it to technical pitfalls of the Coombs test, but this is not in accord with our experience. To guard against technical sources of error inherent in the Coombs test, all possible precautions and suitable controls were included. Also, highly sensitive modifications of the Coombs test were used in most instances. The patients with free auto-antibodies and with negative direct Coombs tests fall into two groups: (1) those who had received corticotropin or cortisone therapy, and (2) those with low titers of auto-agglutinins, frequently detectable with only the most sensitive of the three technics used. The explanation, in our opinion, rests on the use of highly sensitive methods of antibody detection. Testing for free auto-antibodies reduces the incidence of false negative results.

Indication of potency of antibody response. The second argument favoring inclusion of tests for free auto-antibodies in the study of patients with hemolytic anemia is that they may be of value as an indication of the potency of antibody production. In other words, their presence and titer may add to the information furnished by the Coombs test.

Easier technic. Thirdly, there are also technical reasons in favor of testing for free antibodies. The Coombs test has its limitations inherent in its complexity and especially in the difficulty of standardization of the reagent, the antiglobulin serum. That difficulty does not apply to most of the technics used for testing for free antibodies.

Comparative tests. Finally, and fourthly, serum can be stored in the refrigerator for future comparative tests used in following up antibody levels. Specimens of stored serum of different dates can be tested with the same red cells, a procedure which permits better evaluation of results.

Observations Relating to the Pathogenesis of Hemolytic Anemia

The question of the relation between auto-antibodies and the hemolytic process has been the subject of much discussion. Is there a cause and effect relationship between the two or are they merely associated phenomena? One of our cases illustrates pointedly the justi-

fication for the preceding question. A 37 year old woman with acquired idiopathic hemolytic anemia had a strongly positive direct antiglobulin test and free auto-antibodies. Prior to splenectomy the patient received 25 pints of blood, in addition to corticotropin and cortisone, all without relief. After the splenectomy, the anemia improved without further therapy and has remained improved for over three years. In spite of the patient's clinical improvement and the apparent amelioration of the hemolytic process, the titer of the direct Coombs test has remained high, and the titer of free antibodies remained essentially unchanged. It is not surprising that cases like this one invite the conclusion that auto-antibodies are not the cause of the hemolytic process. One could also arrive at a different conclusion, namely, that the antibodies are only one link in the chain that is responsible for hemolysis. It may be that auto-antibodies are preparing the cells for the destruction by the spleen and by other tissues with similar function. Removal of the spleen eliminates the site where the major job of destruction of damaged red cells takes place. This inference would be supported by evidence showing that red blood cells that give a positive Coombs test are functionally inferior to Coombs test-negative red blood cells.

Serologic Changes Resulting from Hormonal Therapy

The effect of corticotropin and cortisone on antibodies has been the subject of much recent discussion. Sharp decrease in the Coombs titer in patients with auto-immune hemolytic anemia following cortisone therapy has been reported. The question most frequently posed is: do these substances inhibit or depress antibody production or do they interfere with the union of the antigen with the antibody? The answer to this question is of more than academic interest. Auto-immune hemolytic anemia offers the unique and excellent opportunity for the study of this problem, because the antigen with or without cell bound antibodies and free circulating antibodies are present simultaneously in this condition.

We have reported previously[7] case histories of patients treated with steroids which showed gradual decrease in the sensitivity of the direct Coombs test, whereas the circulating antibodies persisted for much longer time, though eventually they, too, disappeared.

The interesting feature is that eventually only a particularly sensitive method is able to demonstrate the free antibodies.

These and similar observations suggest that, at least in hemolytic anemia, steroids influence the union of the antigen with the antibody before the antibody production is affected. Doing only a Coombs test on the cells of patients with hemolytic anemia who received steroid therapy may lead to the false conclusion that no auto-antibodies are present, when, actually, free auto-antibodies are still there. It is possible that some statements in the literature to the effect that auto-antibodies have disappeared after hormonal therapy are explained in the light of observations just reported.

Thermal range of auto-antibody reactions. The variations in the thermal reactions of auto-antibodies are of considerable theoretical interest. It is reasonable to assume that there is a reason why in one case the reaction (in titer, intensity and rapidity) is stronger at ice-box temperature, less pronounced or absent at about 20° C., and progressively decreased at lower temperatures. The latter reaction is particularly common in acquired hemolytic anemia. There is reason to assume that each of the two reactions means something different, even if we do not have an explanation at the present time. The term "cold auto-antibodies" should be used for one, "warm auto-antibodies" for the other.

Specificity of auto-antibodies. Another area of confusion concerns the specificity of "auto-antibodies." In most instances, auto-antibodies react not only with erythrocytes of the same person, but also with cells of other persons, including those of the normally inagglutinable group O. There is agreement that auto-antibodies, agglutinins and hemolysins, mean the reaction of the patient's serum with his own red blood cells, but in addition these antibodies react equally well with cells of all blood groups, including the normally inagglutinable O. Actually, in many papers on the subject the authors state specifically that they used only red cells of group O. The implication is that it makes no difference what cells are used and more specifically that there is no particular reason for using the patient's own red cells. This opinion, which seems to have been copied from paper to paper, is not in accord with facts, because it hap-

pens occasionally that auto-antibodies show a selective reactivity. In most instances, they act more vigorously with the homologous cells and less strongly with cells of other persons. This difference may be quite pronounced. Occasionally they react only with the patient's own cells. Rarely, they may react in addition selectively with cells of persons of the same, A, B, O or Rh type.

Nomenclature of hemo-antibodies. There is considerable confusion in terms used in this field of hemo-antibodies. Some writers use the term iso-agglutinins for what others call auto-antibodies. This is unfortunate, because "iso-agglutinin" is recognized as applicable to antibodies reacting in accord with Landsteiner's rules. In other words, an iso-agglutinin in the serum of a person of group A means an antibody reacting with red cells lacking the A factor and possessing factor B. In sharp contrast, auto-antibodies react, as a rule, with red cells of all blood groups. In some cases of hemolytic anemia, auto-antibodies have been observed to react selectively with red cells containing the identical A, B, O or Rh factor. On the basis of this reasoning, auto-antibodies in hemolytic anemia are different from iso-agglutinins.

Some of the confusion in terminology in this and other fields is the outcome of our limited knowledge in general, and of the failure to pay attention to what is known. It is useless to attempt producing a clearly delineated nomenclature prematurely. In a general way, three main varieties of human hemo-antibodies can be recognized at the present time, with unavoidable overlapping in some areas and with haziness and even some contradictions in others. These three varieties, auto-antibodies, iso-antibodies and panantibodies, have each a different significance. They were discussed in greater detail in another paper.[7]

(1) Auto-antibodies react characteristically with the person's own red cells. There are warm and cold auto-antibodies. Erythrocytes of other persons, regardless of blood group, as a rule, are also affected, but various degrees of specificity may be present. It is probable that warm auto-antibodies are the result of auto-immunization or of hetero-immunization. The former may be explained by a change in the red cells, which makes them strange or foreign to the body. In this way, Ehrlich's principle of foreignness to the body (horror autotoxicus) as prerequisite for immunization may be preserved. The transformation of the red cells may be the outcome of various noxious influences. Viruses have been incriminated. Hetero-immunization with bacteria or bacterial products containing antigenic substances present also in human red cells may be responsible, according to Wiener,[8] for formation of antibodies capable of reacting also with red cells. There is reason to consider all hemolysins auto- and hetero-, cold and warm, as the result of immunization.

(2) Iso-antibodies react in accord with rules governing reactions of inherited blood factors. They are present only in persons whose red cells lack the corresponding agglutinogens. They include natural iso-antibodies (reacting best at lower temperatures) and immune iso-antibodies, which may react better at body temperature and which have some characteristics of incomplete antibodies.

(3) The third variety, panantibodies (panagglutinins are better known than panhemolysins), react with red cells of all groups, including the person's own cells, and even with red cells of other species. They are a heterogeneous group and not well defined. Here belong so-called bacteriogenic hemagglutinins resulting from bacterial action. They were first described by Thomsen in contaminated red cell suspensions.[9] Toharsky and I produced panagglutinating properties in serum by growing in it a bacterium *(clostridium hektoenii)*.[10]

The concept of auto-antibodies has been expanded in recent years and has assumed great importance in relation to thrombocytopenia and leukopenia. A reduction of platelets or granulocytes followed injection of blood from a person with thrombocytopenia or granulocytopenia into a normal recipient. The leuko-agglutinin has been defined clearly as an auto-antibody and its action has been observed in an impressively large number of cases by reliable investigators. Its association with leukopenias has been established. In the occasional cases in which it was found in patients with leukocytosis, the individual had a history of many transfusions, which could explain the origin of the antibody.

There is reason to hope that the fruitful concept of auto-antibodies may help to clari-

fy some hitherto unexplained puzzles in medicine.

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The Use of Nitrogen Mustard in the Treatment of Lymphoblastomas*

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In recent years the addition of new drugs and hormones to our therapeutic armamentarium permit a more comfortable prolongation of life in those suffering from one of the lymphomas.

THE USE of nitrogen mustard in the treatment of lymphoblastomas developed as a by-product of a systematic study of the mustard gases during World War II by the Chemical Warfare Service of the United States Army. When it was shown by Goodman and Gilman, and by Dougherty that parenteral administration of aqueous solutions of nitrogen mustard produced lymphocytopenia and modified the changes of spontaneous leukemia and lymphosarcoma in rats, the drug was tried in instances of various malignant diseases in man.

Results of the combined efforts of many clinical investigators over the past 10 years permit us now to draw some conclusions regarding the role of nitrogen mustard in the treatment of lymphoblastomas.

The nitrogen mustard which has found the widest use is methyl-*bis* (β-chloroethyl) amine hydrochloride, generally abbreviated HN_2. This drug has cytotoxic effects very similar to x-ray and it is of value only in conditions where x-ray therapy is of value. In fact, it is best considered an adjunct to irradiation and not as a drug to replace treatment by x-ray.

Indications for Treatment

Hodgkin's Disease. Nitrogen mustard is of the greatest value in this disease. The indications for the use of HN_2 are the best when: (1) the disease is generalized, particularly when fever and toxicity are present; (2) the disease appears to be resistant to x-ray treatment; and (3) there is intractable pruritis. When there is generalized involvement plus large localized areas of lymphadenopathy, it is best to follow HN_2 therapy within one to two weeks by localized x-ray treatment.

Nitrogen mustard is also of value in *mycosis fungoides* and in *lymphosarcoma* with generalized spread of the disease. It is often effective in *chronic myelocytic* and *chronic lymphocytic leukemias,* and *giant follicle lymphoma,* but in my opinion other forms of therapy are preferred in these diseases.

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The drug, though not very encouraging in the treatment of *reticulum cell sarcoma,* may produce an impressive temporary improvement, and is sometimes the treatment of choice in this disease.

Effect on Blood Picture

It should be remembered that nitrogen mustard is a dangerous drug which, when administered in excess, may produce permanent aplasia of the bone marrow. The usual changes in the blood picture should be kept in mind when this drug is administered.

There is a gradual decrease in hemoglobin and hematocrit during the first few days after therapy with a gradual return to previous levels. In fact, in anemic patients, a favorable response is demonstrated by rise in hemoglobin to normal. A slight initial rise occurs in platelets followed by a progressive fall reaching the lowest point, three to four weeks after injection. There is a progressive fall in the white cell count with the lowest count occurring at two to three weeks after which there is a gradual return.

Use of Nitrogen Mustard

Dosage. Nitrogen mustard is best given in a total dose of 0.4 mg. per kilo of weight, or less. This may be given in a single dose, or in divided doses. Although there are theoretical advantages to giving the mustard in four divided doses, there are several practical advantages to giving it in a single dose, or in two doses.

Administration. Nitrogen mustard comes in vials containing 10 mg. This should be diluted with 10 cc. of saline solution just before use. The appropriate dosage is injected immediately into the tubing of a freely flowing intravenous infusion of saline. Experimental studies have shown that the mustard begins its effect in less than five minutes after injection.

Premedication. The frequent occurrence of severe nausea and vomiting, formerly a common objection to the use of nitrogen mustard, can now usually be effectively controlled by 50 mg. Thorazine intramuscularly 30 minutes before the injection of mustard. Supplemental barbiturate sedation should be in small dosage because of the potentiating effect of Thorazine.

Favorable effects of nitrogen mustard include a decrease in toxicity, decrease in fever, improvement in appetite and well being, a rise in hemoglobin, a decrease in lymph adenopathy, decrease in effusions, and decrease in itching. The degree of response varies greatly.

Recent considerations include the injection of 0.4 mg. per kilo of weight of HN_2 directly into pleural or ascitic fluid in the treatment of effusions associated with Hodgkin's disease. Evidence has been presented by Weisberger of Western Reserve that the preliminary administration of 15 Gm. of L-cysteine may prevent the leukopenic changes of nitrogen mustard without altering the favorable response of the Hodgkin's disease itself. These considerations require further evaluation.

Renal Complication. A final precaution is necessary. Following the use of nitrogen mustard, particularly in lymphosarcoma and leukemia, there is danger of urinary tract obstruction by the precipitation in the kidney and ureters of uric acid crystals, resulting from the rapid breakdown of tissues. This may be prevented by a high fluid intake and alkalinization of the urine by the administration of 8 to 12 grams of sodium bicarbonate daily in divided doses.

Triethylene Melamine Therapy in the Lymphomatous Diseases*

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THE EFFECT of triethylene melamine (TEM) on normal and malignant tissues is similar, if not identical, to that of the common nitrogen mustard compound, methyl-*bis*-(2 chloroethyl) amine hydrochloride. The reactive groups of both compounds are the terminal ethyleneimino ring structures (Fig. 1). Two or more of these groups are necessary for antileukemic effects. They are thought to react in the tissues with many proteins and cellular constituents.

Two pharmacologic properties of TEM are responsible for its unique practical usefulness: (1) it can be given by mouth, and (2) in proper doses it produces few or no troublesome side reactions. The dosage with oral administration unfortunately varies considerably from patient to patient. The chief hazard of using TEM is inadvertently producing a severe, temporary depression of bone marrow function.

Therapeutic and Untoward Effects

The qualitative effects of TEM in different types of lymphoid malignancies may easily be illustrated. Lymph node tumors in patients with Hodgkin's disease may largely disappear after four to six weeks of effective therapy. In those with generalized disease, fever and leukocytosis subside as appropriate amounts of the chemical are given and anemia begins to regress. In patients with lymphocytic lymphoma masses of lymph nodes often disappear completely in two to three months. In the majority of patients with chronic lymphocytic leukemia, the excessive proliferation of lymphoid tissue in nodes, liver, spleen and bone marrow can readily be suppressed.

Despite these attractive potentialities, however, many authorities consider that TEM is too dangerous to use. Unless dosage problems can be solved by the physician using it, an effective amount of the chemical may not be given or an undue risk may be assumed. Although the dosage of the chemical varies considerably from individual to individual, we have found that with strict precautions regarding dosage and mode of administration, as outlined below, the chemical can be used safely. Early in our use of it about one patient in ten was given an excessive amount. During the last two to three years in a large number of patients treated by different members of our staff, serious overdosage has not occurred. In reference to possible late complications, such as gonadal atrophy, endocrine disturbance, susceptibility to infection, serum protein abnormalities, and the like, these have not been unduly frequent even among patients who have been maintained on TEM for three to five years.

It must be emphasized that the dose of TEM has to be determined individually. The extent to which it is absorbed apparently varies considerably from patient to patient. The chemical is destroyed by acid and by contact with food. Tablets should always be given, accordingly, to patients who are fasting an hour or more before breakfast and with at least 2 grams of sodium bicarbonate to neutralize gastric acidity. In initiating therapy, the maximum safe dosage is 2.5 mg. given on each of two successive mornings. About one patient in 15 to 20, being extremely sensitive to the effect of the chemical, will develop anorexia 8 to 12 hours after the second dose.

It is necessary to distinguish possible gastrointestinal symptoms due to the ingestion of sodium bicarbonate, which develop within a few minutes, from the more delayed effects of TEM. If the second dose does not pro-

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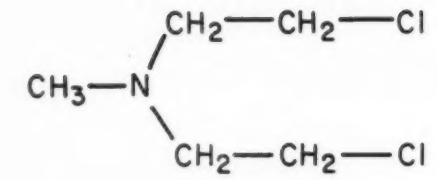
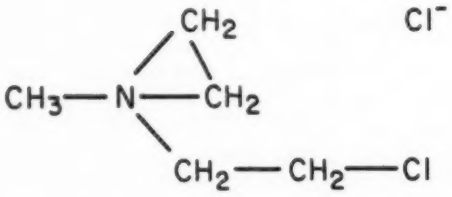
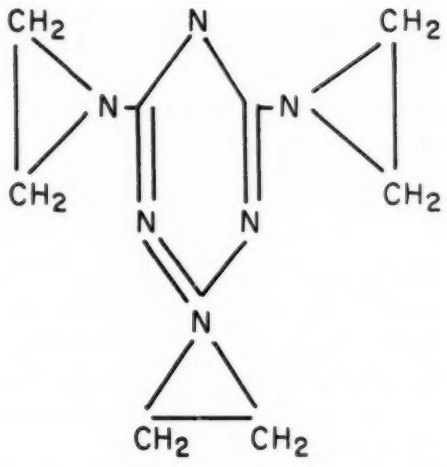
FIG. 1



Methyl bis
(B-chloroethyl) amine
(nitrogen mustard)



Ethylenimonium transformation
of nitrogen mustard



Triethylene melamine
(TEM)

Comparison of chemical structure of nitrogen mustard compound, its transformation product in solution, and triethylene melamine.

duce anorexia, it is usually safe to give a third 2.5 mg. dose. The effect of the initial doses on appetite and white blood count must then be observed for three to five days before giving more of the chemical.

Patients can be classified as to grades of sensitivity to TEM by observing the effect of the initial two or three doses. (1) *Maximal sensitivity* is shown by those who develop anorexia or a fall in white cell count after the first two 2.5 mg. doses. The maintenance requirement for these patients will be only 0.5 to 1.0 mg. every 7 to 14 days. (2) *Average sensitivity* includes those who develop anorexia after the third 2.5 mg. dose, and/or a fall in the prevailing white cell count within three to eight days. The maintenance requirement in this group will be 1.0 to 2.5 mg. every 5 to 10 days. (3) *Low sensitivity* is shown by patients who have no observable effect from the first three 2.5 mg. doses. These patients may require 2.5 or even 5 mg. of TEM every two to five days for effective maintenance chemotherapy. In individual patients TEM dosage requirement remains relatively constant year after year.

Therapy should be suspended whenever the white cell count falls rapidly until it stabilizes. The full effect of given doses may not be evident for 7 to 10 days. Any dose that causes severe anorexia or vomiting is excessive. In patients with continuously active disease, fully effective chemotherapy requires the constant maintenance of a slight leukopenia. If carefully managed the latter may be achieved without risking cumulative effects, diminishing resistance to infection, etc.

Management of Lymphomatous Disease

Lymphoid tissues are most sensitive to the growth suppressive effects of TEM, and the chemical has proved to be a most useful therapeutic agent in the management of malignancies of this origin. The practicality and convenience of TEM therapy has permitted revisions in practical therapeutic strategy. At this time we believe the frequently quoted therapeutic tenet, to withhold treatment until patients have obvious symptoms which need palliation, is obsolete. Better results can be obtained if a program is designed as early as

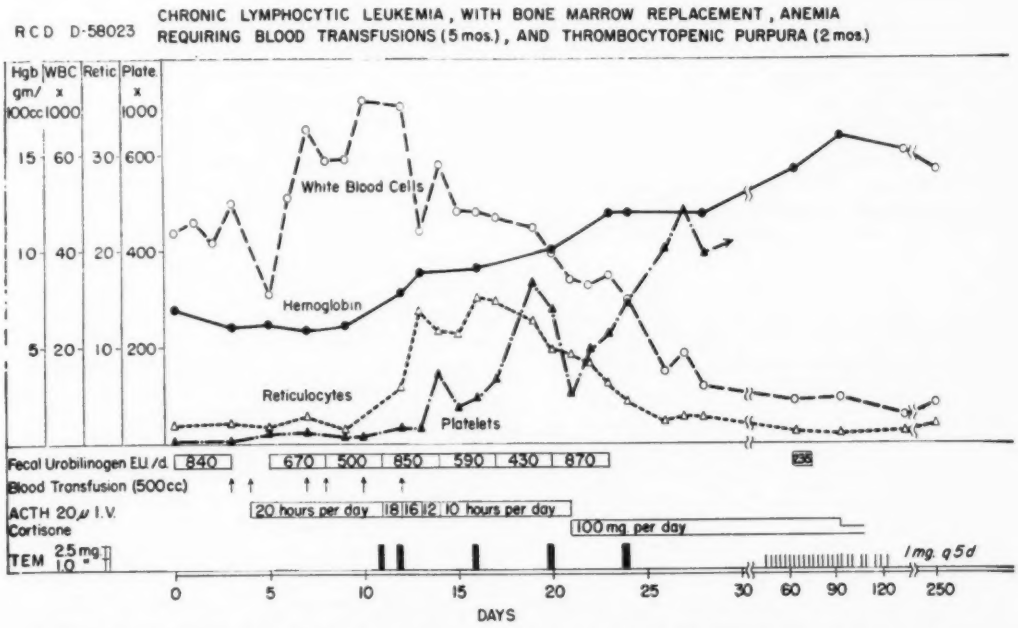
possible to control the entire disease process. The natural history of the malignant lymphomas is for the abnormal cellular growth to become more generalized anatomically, and more malignant. Many foci of disease remain hidden during life. Different agents are used in accordance with the selectivity with which they suppress the growth of particular cells and according to the anatomic problems involved. Our present policies regarding the management of malignancies arising from the lymphoid tissues can be summarized as follows:

Chronic lymphocytic leukemia, the commonest of all types of leukemia, develops in the later decades of life. It occurs in different degrees of malignancy, with or without conspicuous enlargement of lymph nodes, hepato- or splenomegaly. While the median survival is three to four years, the mortality during the first year is 20 per cent and only about 5 per cent of patients survive 10 years. The disease is often far advanced before symptoms become particularly troublesome. Late complications relate for the most part to bone marrow damage, anemia, infection and/or hemorrhage. Hemolytic anemias are not infrequently associated with the uncontrolled disease.

The conventional therapy of past decades, roentgen irradiation to enlarged nodes or organs when health becomes impaired, appears to alter the natural course of the disease very little. Regularly spaced "titrated" whole body irradiation or treatment with P^{32} promises to give better long term results (Osgood).

The results of TEM chemotherapy are most promising in chronic lymphocytic leukemia. Patients with this disease tend to be more sensitive to its effect than others. In the great majority of patients lymphocytic leukocytosis, lymph node enlargement, hepato- and splenomegaly regress promptly, and with appropriately maintained therapy can be controlled for years. The selectivity of the TEM effect is most convincingly demonstrated by the reversal of bone marrow infiltration and/or replacement with abnormal lymphocytes. Unless bone marrow damage has become too severe, normal myeloid ele-

FIG. 2



Hematologic response of a patient with chronic lymphocytic leukemia and severe pancytopenia, resulting from bone marrow replacement developing during the first year of disease, despite irradiation therapy. With ACTH therapy, followed by cortisone and TEM an excellent remission ensued which was maintained for two years. A leukemic exacerbation then led to fatal termination, three and one-half years after onset of the disease.

ments regenerate as the lymphocytic overgrowth is suppressed and anemia regresses.

Our present policy in the treatment of lymphocytic leukemia is to begin TEM therapy as soon as the diagnosis is made and maintain it without interruption, attempting to suppress as completely as possible all manifestations of disease. The long term results and complications of this program are under study.

In patients with unusually aggressive lymphocytic leukemia which cannot be controlled with TEM alone, or in those in whom serious bone marrow damage already has occurred, ACTH and the adrenal steroids are most useful in addition. The plan of therapy combining these agents is illustrated in figure 2.

Malignant lymphomas of various histologic type (giant follicular, lymphocytic, lymphoblastic, lymphosarcoma, reticulum cell sarcoma, etc.) cannot be sharply separated from lymphocytic leukemia, except for a greater tendency for them to remain localized. When the proliferation involves relatively mature lymphocytes, the results of TEM chemotherapy alone may be excellent. With more primitive and malignant cellular growth, less is generally accomplished. In these patients, if the disease is anatomically circumscribed and away from vulnerable areas such as the bone marrow, local roentgen irradiation may be used most effectively. In the majority of patients with malignant lymphomas, however, the combination of local irradiation and TEM therapy gives a superior result. The administration of steroid hormones is often of additional benefit as it is in chronic lymphocytic leukemia.

In *Hodgkin's disease* the most complete and lasting antitumor effects are produced by roentgen irradiation. The importance of early and aggressive therapy in those with localized and potentially curable lesions has been emphasized in recent years. Chemotherapy alone is usually ineffective in controlling Hodgkin's disease although exceptions occur. Our present policy is to supplement the effects of local irradiation with maintenance TEM therapy in all patients with widespread, occult or frequently recurring lesions. It is our impression that the additional use of chemotherapy is of considerable value in prolonging the health and longevity of many patients. Adrenal steroids appear to be of little benefit in Hodgkin's disease.

Conclusions

The tissue effects of TEM and the nitrogen mustards are similar. The practical advantages of TEM are oral administration and the absence of troublesome side reactions. The chief hazard of TEM therapy, serious depression of bone marrow function, is due to the wide variation in its apparent absorption from patient to patient. The chemical can be used safely and effectively, however, by carefully individualizing the dose. TEM is a most efficient agent in the control of chronic lymphocytic leukemia and lymphocytic lymphomas. It is a valuable adjunct to irradiation in the treatment of other malignant lymphomas and Hodgkin's disease.

The Treatment of Lymphomas with Adrenocortical Substances*

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THE PURPOSE is to discuss the relative importance and indications for the use of cortical steroid hormones in the treatment of the lymphomas. Every discussion of lymphomas must be based on a common speaking ground or classification. We recognize that this has been a knotty problem over a number of years. For the purpose of this presentation, we will use the classification presented by Berman[1] (Table 1).

We have seen in the Veterans Administration Hospital, at Houston, over a five-year period, a total of 73 cases listed with apparent indications for the use of steroids in 36 cases. Steroid therapy was used in one-half of the lymphoblastic types. This is a reflection only of the availability of steroids since they were used in all cases occurring in the last three years. In the lymphocytic and mixed types of lymphomas, steroids were used in one-half the cases but prescribed on the basis of specific indications.

Indications for Hormonal Therapy

Let us consider the indications for the use of steroids. It may be well to reflect for a moment upon the physiologic basis for the use of these compounds in the treatment of lymphomas. It is an old observation that adrenalectomy results in some hypertrophy of lymphatic tissues. Likewise Murphy and Sturm[2] observed that the administration of adrenocortical extracts resulted in an involution of lymphatic tissues. They extended this observation to show that transplanted mouse leukemia was favorably influenced by the use of adrenocortical extracts.[3] Several attempts to apply this information clinically resulted in failure. When it became possible to administer larger doses of purified materials, Pearson, Eliel and Talbot[4] undertook a clinical trial and demonstrated a favorable response among certain of the lymphomas. These studies thus demonstrate that a simple involution of lymphatic tissue may be produced by the adrenocortical or hormones. There have been a few demonstrations of reversion of the bone marrow of lymphoblastomas to normal as reported in the use of antimetabolites as aminopterin (4-aminopteroylglutamic acid).[5]

A second property of the adrenal cortical steroids of interest in this regard may be called their anti-inflammatory effect. Many studies have now been recorded to show the inhibitory effects of cortical steroids upon the immune response at the tissue level. That is not in the circulating antibody-antigen reaction but in those partial antibodies fixed to cells, as in the auto-immune reactions associated with acquired hemolytic anemia and some thrombocytopenias. Resolution of these auto-immune agents is effected by the steroid.

Associated with the general anti-inflammatory activity of the cortical steroid is an antipyretic property. This is of importance in the general support of the patient through Pel-Ebstein fever.

Case 1. This 56 year old, white man was reported to be in good health until 32 months prior to ad-

TABLE 1

CLASSIFICATION OF MALIGNANT LYMPHOMAS AND NUMBER TREATED WITH STEROID HORMONES

Type	*Number of Cases*	*Steroid Therapy*
I. Reticulum cell	3	1
II. Lymphoblastic	12	6
III. Lymphocytic	19	10
IV. Mixed		
A. Hodgkin's	36	18
1. Paragranuloma		
2. Granuloma		
3. Sarcoma		
B. Follicular		
1. "Pre-blastomoid"		
2. Diffuse blastomatous	3	1
Total	73	36

*Read before a joint session of the Sections on Medicine and Pathology of the Southern Medical Asosciation, Forty-Eighth Annual Meeting, St. Louis, Mo., November 8-11, 1954.

mission. At this time he noticed weakness, fatigability and shortness of breath. His physician made the diagnosis of *chronic lymphatic leukemia.*

He was admitted to a hospital where he received x-ray therapy, transfusions and ACTH. Intermittent hospitalizations approximately every three months had been necessary for transfusions. However, in the 30 days prior to the present hospitalization he had received a total of 42 pints of blood. Icterus had been intermittently present for approximately seven weeks.

Physical examination revealed pallor, icterus, and lymphadenopathy in all the superficial chains. The spleen extended to the crest of the ilium and the liver extended four finger-breadths below the costal margin at the midclavicular line.

The *laboratory studies* included a hematocrit of 18 per cent, hemoglobin of 6.5 Gm., erythrocyte count of 1.96 million, leukocyte count of 3,250 with 11 per cent neutrophils, 86 per cent lymphocytes and 1 per cent eosinophils. This patient had a positive Coomb's test indicative of acquired hemolytic anemia; cold agglutinins and iso-agglutinins were not demonstrated.

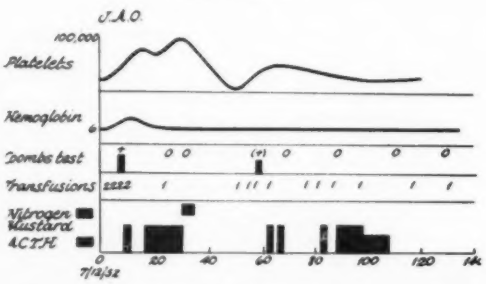
Course. The patient received transfusions, nitrogen mustard and ACTH. The Coomb's test became negative following the administration of ACTH and continued to be negative for some weeks thereafter. When it became positive again, further administration of ACTH resulted in a negative test. Also of note is that while he did not obtain a marked rise in platelets, nor a marked reticulocytosis, and increase in the red count, the need for transfusions decreased significantly and the icterus cleared (Fig. 1).

We believe that in this patient, acquired hemolytic anemia secondary to chronic lymphatic leukemia was alleviated and the patient's course markedly improved by the adjunctive treatment with ACTH.

The next case demonstrates the resolution of lymphatic masses by the use of cortical steroids.

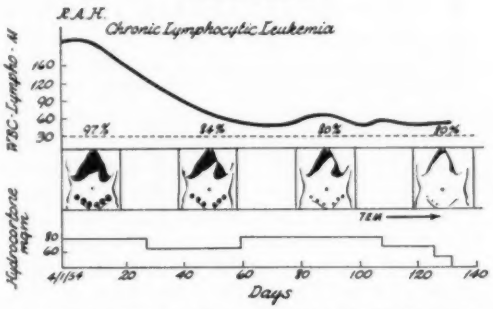
Case 2. This is a 60 year old white man, a moving picture machine operator, had noticed intermittently for six years that he tended to bleed rather easily.

FIG. 1, CASE 1



Chronic lymphatic leukemia with acquired hemolytic anemia as a complication. Effectiveness of ACTH in controlling hemolysis is demonstrated by the decreased frequency of transfusions to maintain patient's hemoglobin.

FIG. 2, CASE 2



Chronic lymphatic leukemia in which lymphadenopathy and hepatosplenomegaly had reached a distressing degree. Hydrocortone caused regression which was further aided by a short course of TEM. Maintenance by Hydrocortone alone for more than one year.

Several weeks prior to admission he had painful swelling of his wrist joints. He had occasional night sweats and developed a nonradiating epigastric distress which was apparent on walking and relieved with rest. He was seen in the VA Regional Office in San Antonio, where a diagnosis of *chronic lymphatic leukemia* was made.

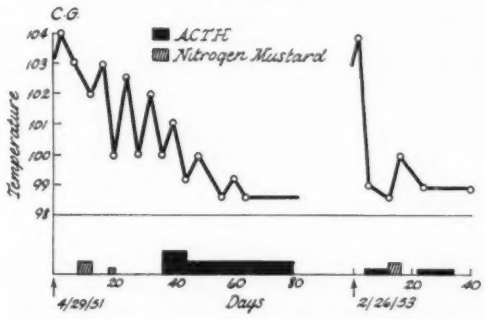
Physical examination revealed a well developed white man with a temperature of 98.6, pulse 96, respirations 20, blood pressure 160/80. There was moderate obesity. There were a few raised macular lesions of the face and the skin of the neck. There were palpable cervical, axillary and inguinal lymph nodes. The inguinal nodes were particularly enlarged being approximately 3 cm. in diameter and extending along the inguinal ligaments and into Hunter's canal. The chest was clear to percussion and auscultation; the heart was not enlarged; the abdomen was protuberant, the liver and spleen were enlarged extending to the crest of the ilium.

Blood studies included a hemoglobin of 15.6 Gm., erythrocyte count of 5.23 million, leukocyte count of 175,750 with 97 per cent lymphocytes, 2 per cent neutrophils and 1 per cent monocytes. Coagulation studies were within normal limits. Platelet count was 160,000.

In view of the patient's desire to be released promptly from the hospital, and in the absence of anemia, it was felt that a form of therapy which might produce resolution of his lymphatic masses without toxic reaction upon the normal hemopoietic tissue would be in order. The patient has been followed intermittently and has had a progressive decrease in the size of the spleen and the liver. Recently the patient has received triethylene melamine and continues in his work. He has continued without enlargement of nodes or spleen for one year taking only 60 mg. of Hydrocortone (Fig. 2).

This case is presented to demonstrate the inhibitory effect of cortical steroids on lymphatic activity. It has been a convenient and economical method of handling this patient's illness and has not required prolonged periods of hospitalization.

FIG. 3, CASE 3



Hodgkin's disease in which Pel-Ebstein fever had produced marked debility, controlled only briefly by x-ray and nitrogen mustard. ACTH therapy over a 7 week period controlled this and other manifestations.

Case 3. This 27 year old white man was admitted to the hospital because of fever and arthritis. He said that in the six months prior to his first admission, in June, 1950, he had had intermittent episodes of arthritis. In the two months prior to admission, night sweats and fever had recurred frequently.

Physical examination revealed a pale, thin white man, with motion of the joints limited in the wrists, and there was acute diffusion and retinus. There was some pain on flexion of the elbows and wrists, and some tenderness and moderate effusion in both knees. Superficial lymph nodes were palpable in the cervical, axillary and inguinal areas varying from 0.5 to 2 cm. in diameter. The chest was clear to percussion and auscultation, the heart of normal size, the abdomen scaphoid with the palpable spleen 3 cm. below the costal margin on deep inspiration. This patient received two courses of nitrogen mustard with resolution of the lymphoid masses and fever, and subsequently improvement in the arthritis. Upon recurrence of fever one year after his first admission, x-ray therapy was directed to the spleen. There was transient improvement.

On April 29, 1951, the patient was admitted with Pel-Ebstein fever which had been present for approximately three weeks. A course of nitrogen mustard was given with little improvement in his septic course. ACTH was begun and a progressive lysis of the fever followed. Upon recurrence of fever, the administration of ACTH prior to nitrogen mustard again resulted in lysis of fever. Since this episode he has had but one reactivation of the disease, at which time 10 mg. of ACTH intravenously over an eight hour period for three days controlled the fever. The patient is sustained on 60 mg. of Hydrocortone with little activity of the Hodgkin's disease or his rheumatoid arthritis (Fig. 3).

This case then illustrates the antipyretic activity as part of the anti-inflammatory influences of steroid hormones.

Discussion

A comment is in order concerning doses and precautions to be used in the employment of steroid hormones. It will be noted that in each of these patients, rather large doses of ACTH or cortical steroids have been prescribed. It has been our experience that this is necessary to control lymphomas.

Doses of ACTH have varied between 10 and 20 mg. administered by slow intravenous infusion over an 8 to 12 hour period. This dose is probably equivalent to 200 to 400 mg. administered intramuscularly. When intramuscular doses have been used, they have varied from 20 to 60 mg. every four hours. Cortical steroids have been used in doses of 20 to 400 mg. per day. As a rule, Hydrocortone is the preferred steroid and the average dose is approximately 120 mg. per day given in six divided doses. With these extreme doses, symptoms of Cushing's syndrome appear and the physician must be alert to the complications of this disease. He should restrict the sodium intake, add to the potassium intake, provide adequate protein and ascorbic acid. He should be alert to evidences of hypokalemia, hypochloremia and acute sodium retention. The latter is especially important in older individuals with sclerotic heart disease, as acute pulmonary edema will develop. Decrease in glucose tolerance is not uncommon, but is usually not of importance unless the patient has a predisposition to diabetes. It should be stated that Cushing's syndrome is not a contraindication to continued steroid therapy in these situations. In the acute leukemias, steroid therapy should be continued and, if effective, is usually heralded by an increase in the platelet count and the reappearance of normal elements in the peripheral blood. Remissions are apt to be brief, varying from 2 to 12 weeks in duration and in children it is commonly advised now to use steroid therapy with antimetabolites as aminopterin or 6-mercaptopurine. The experience reflected in this group of cases with acute leukemias is not a basis for estimating the effectiveness of steroid therapy. It may be stated that the experiences of Burchenal[5] and others suggest that approximately one-third of the cases of acute leukemias in children will show a brief remission.

In addition to the hazards of purpura occurring in this group of diseases, the cortical steroids result in increased gastric acidity.

TABLE 2

MANIFESTATIONS OF LYMPHOMAS AND THEIR RESPONSE TO THERAPY

Lymphoma Type	*Fever*	*Purpura*	*Thrombocytopenia*	*Nodes*	*Symptom*
Reticulum cell	1/1 100%	0	0/1 0%	0	...
Lymphoblastic	5/5 100%	2/4 50%	0/5 0%	0	50%
Lymphocytic	3/3 100%	3/5 60%	6/7 85%	2/10 20%	60%
Mixed types					
Hodgkin's	13/17 76%	2/3 66%	4/9 44%	0	50%
Follicular	1/3	0/1	0/1	0	100%

Number of cases treated and response in percentage in each category.

Therefore, the development of peptic ulcer symptoms should receive prompt attention and treatment, since perforations and hemorrhage have been reported commonly.

The principal indications for use of adrenocortical steroids have been fever, purpura, thrombocytopenia, the enlargement of lymphatic masses and for symptomatic improvement (Table 2). Among the lymphatic leukemia cases in adults, we observed that fever resolved in all cases, the purpura was improved to 50 or 60 per cent, thrombocytopenia was not improved in the acute cases, whereas some improvement was observed in the lymphocytic cases. In two of the chronic lymphatic cases there was considerable significant resolution of the lymphadenopathy. In approximately 50 or 60 per cent of the cases, symptomatic improvement was obtained. In the Hodgkin's disease group, which makes up our largest clinical experience, resolution of fever was an important contribution to the symptomatic improvement and to the nutritional improvement of the patient so that more definitive therapy could be carried out. This occurred in 76 per cent of those cases in which cortical steroid therapy was prescribed. Our experience with purpura in this group is somewhat limited with two of three cases showing a significant improvement. Thrombocytopenia presumably in part on an immunohematologic basis improved in four of nine, or 44 per cent of the cases. Fifty per cent of these patients showed marked symptomatic improvement. In the one individual with giant follicular lymphoblastoma significant improvement in symptoms resulted.

Use of Other Agents. It is apparent from this discussion that the adrenocortical steroids are an adjunct to the treatment of lymphomas. They are not to be considered the primary treatment in any of these diseases. In the case of reticulum cell sarcoma, roentgen therapy is the treatment of choice. In the acute lymphoblastic types the use of metabolic antagonists, as Purinethol (6-mercaptopurine) and Methotrexate must be considered the treatment of choice. In the lymphocytic group the use of roentgen therapy, nitrogen mustard or radioactive materials may be considered. In our experience the use of a nitrogen mustard compound and roentgen therapy have been most commonly used. In the control of mixed types such as Hodgkin's disease, we have followed a similar pattern of clinical management. We have not in any of these cases used steroids as our primary mode of therapy.

Summary

In summary, in a group of 73 cases of lymphomas indications for steroid therapy occurred in 36 or approximately in 50 per cent. These indications included the control of fever, the resolution of auto-immunohematologic reactions such as thrombocytopenia, purpura and acquired hemolytic anemia, and as an adjunct in the resolution of lymph nodes. Significant symptomatic improvement may be obtained following the use of adrenocortical steroids, which may in turn so improve the patient's general condition so as to permit more definitive therapy. Adrenocortical steroids are not to be considered a primary mode of treatment in the control of malignant lymphomas.

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Transaminase and C-Reactive Protein Levels in Acute Myocardial Infarction: Evaluation of Indices of Necrosis

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The authors review the various types of blood studies which have been proposed as aids in the diagnosis of myocardial infarction. They present their results in applying the determination of serum transaminase in this lesion.

Introduction

THE DIAGNOSTIC INNOVATIONS for the acute myocardial infarction have almost all been in the field of electrocardiography since the original description of this entity by Herrick 43 years ago.[1] The electrocardiogram is merely a study of electrical impulses and as a result it is at times inadequate for the establishment of a definitive diagnosis in acute myocardial infarction. In the last few years, studies by many investigators have unveiled a host of alterations in the blood of patients who have recently sustained such an attack. For the most part, these changes are nonspecific and hence not necessarily a reflection of myocardial metabolism.

Recently, LaDue, Wroblewski and Karmen have developed better methods for the detection of serum glutamic oxaloacetic transaminase,[2, 3] an enzyme which is widely distributed in human tissues and heavily concentrated in the myocardium. They observed transient elevations after myocardial infarction. We have employed this test on patients who were admitted to the hospital complaining of pain characteristic of myocardial disease. An attempt has been made to correlate the results of this test with the clinical findings, including the electrocardiogram and other blood studies suggesting the presence of tissue damage.

Material and Methods

This series consists of 18 patients who were admitted to Vanderbilt Univeristy Hospital with the chief complaint of chest pain, the characteristics of which were strongly suggestive of coronary artery disease. There were 13 males varying in age from 39 to 72, and 5 females with an age range of 55 to 71 years. In only an occasional instance did these patients have minor complicating illnesses which could be associated with a significant amount of tissue destruction. Five of the individuals studied had a past history of proven myocardial infarction.

Eighty-four blood specimens were drawn for analysis at various time intervals, without regard for the fasting state, during the first few days after hospitalization. In all but four instances the initial specimen was obtained within 42 hours and in five instances within 8 hours after the onset of pain. When feasible, samples were taken every 4 hours during the first 24 hours of hospitalization.

Erythrocyte sedimentation rates, white blood counts, C-reactive protein analyses and transaminase values were obtained on each blood specimen.

All samples were obtained through a 20 gauge needle, with a dry autoclaved syringe. Care was taken to avoid hemolysis and the blood was allowed to clot*; this was carefully dislodged from the walls of the tube and centrifuged at medium speed for 15 minutes. Serum was aspirated and placed in the deep freeze and C-reactive protein determinations were made with C-reactive protein antiserum** using the method described by Anderson and McCarty.[8]

Transaminase activity was measured by the method of Karmen, Wroblewski and LaDue[3]

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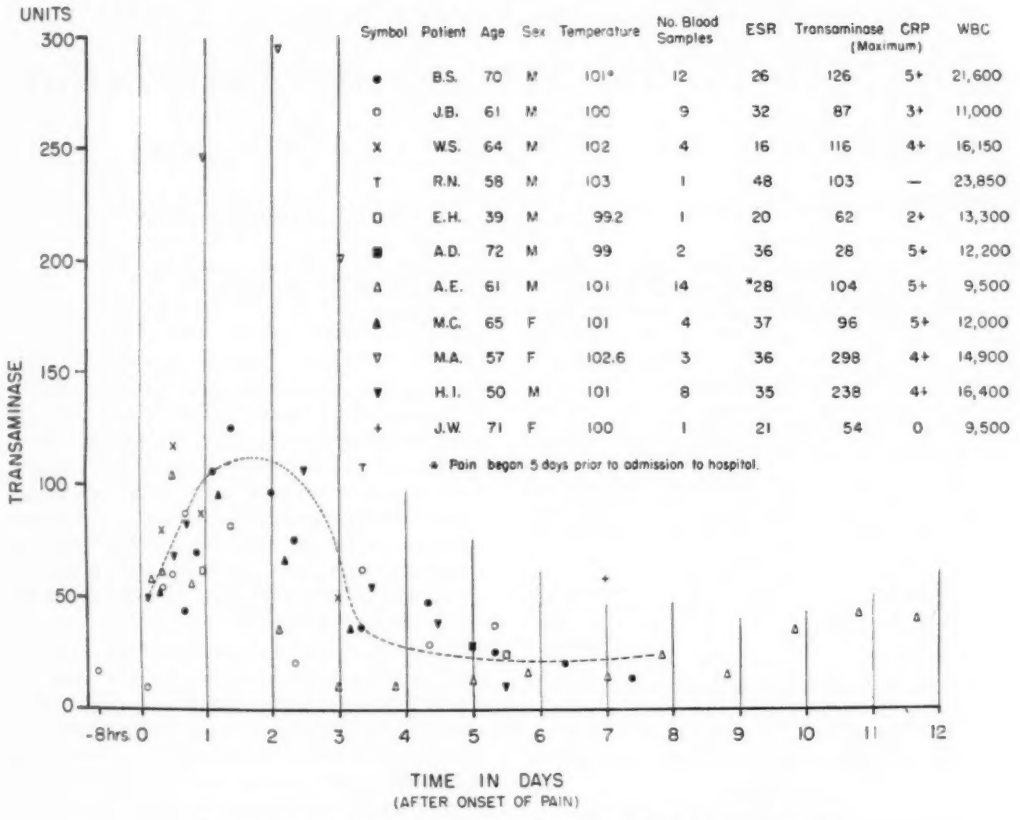
*Many patients were taking dicumarol and had a prolonged clotting time.

**Supplied by Schieffelin & Company.

FIG. 1



Composite graph and chart of patients with proven myocardial infarction (Group I).

as modified by Kattus.[24] The reaction is as follows:

1. Aspartate + a-ketoglutarate $\xrightleftharpoons[\text{pyridoxal phosphate}]{\text{transaminase}}$ Glutamate and oxaloacetate
2. Oxaloacetate + DPNH + $H^+ \rightleftharpoons$ malate and DPN+

The coenzyme pyridoxal phosphate is supplied sufficiently in serum and the reagents are added in excess, resulting in serum transaminase being the limiting factor. The transamination reaction then is coupled to a second reaction in which oxaloacetate is reduced to malate and in the presence of reduced diphosphopyrodine nucleotide and malic dehydrogenase. The rate of oxidation of $DPNH_2$ is followed at a wave length of 340 mu on the Beckman DU Spectrophotometer.

Since maximal activity for transaminase is between a pH of 7.0 and 8.0, the reagents are prepared in a phosphate buffer with a pH of 7.5. All the reagents are at room temperature except $DPNH_2$ and malic dehydrogenase which are kept in an ice bath but appear in only minute amounts in the mixture.

The malic dehydrogenase* is obtained as a colloidal solution without definite standard of activity and is diluted 1:10 with phosphate buffer.

Two-tenths of a milliliter of serum, 1.0 ml. of 0.0715 M asparate, 0.1 ml. of malic dehydrogenase, and 0.1 ml. of $DPNH_2$ (2 mg./ml. of buffer) are shaken together and incu-

*Obtained from The California Foundation for Biochemical Research.

bated at room temperature for 10 minutes in a Beckman cuvette.

Then 0.2 ml. of 1M-alpha-ketoglutarate is added. There follows a rapid decline in absorption at 340 $m\mu$, indicating the initiation of the transaminase reaction.

The blanks contained all the aforementioned constituents except $DPNH_2$. Readings are taken every minute and a linear curve is plotted. Results are expressed in units per ml. of serum. One unit is that amount of transaminase present in 1.0 ml. of serum which will cause an optical density decrease of 0.001 units in one minute.

Results

The patients in this series are divided into three categories in accordance with the findings on serial electrocardiographic tracings. There were 11 patients who had proven myocardial infarctions (7 of whom died in the hospital), 4 who had equivocal electrocardiographic tracings, and 3 who had only minimal changes in the electrocardiographic tracings (Fig. 1). There were seven anterior and four posterior myocardial infarctions. All patients were admitted to the hospital because of chest pain suggestive of myocardial disease. There were no acute complicating illnesses in any of the patients studied.

All but one of the patients who had proven myocardial infarctions developed fever during their hospital stay. Two patients in Group II and one patient in Group III developed fever.

The erythrocyte sedimentation rate was elevated in 10 of the 11 patients in Group I and the white blood cell count was elevated in 9. There seemed to be no gross correlation between the degree of elevation in the white blood count and the magnitude of the increase in the erythrocyte sedimentation rate.

The C-reactive protein was present in every patient in Group I in whom the first specimen was taken before 7 days after the infarction. It was usually present in the first blood sample although in some its appearance was delayed several hours.

The glutamic oxaloacetic transaminase level in the serum was increased in all but one of the patients who had proven myocardial infarction. The first serum level in this patient (A.D.) was drawn 5 days after the outset of pain. Seven of these patients had blood drawn within the first 24 hours, in most cases at frequent intervals (normal range is 10 to 40 units). In some cases the transaminase level was elevated within 4 hours after the onset of pain.

A mean transaminase level curve is plotted from the levels taken on the 11 patients with proven infarction (Fig. 1). The average rise began in the first few hours and reached its peak at one and a half days. This average level was normal again (i.e. 10 to 40 units) at three and a third days.

One patient demonstrated a normal transaminase level again at 51 hours. One value was still elevated on the seventh day.

The serum C-reactive protein became elevated in all but one of 10 patients tested in Group I (Fig. 1). This patient (J. W.) had a slightly elevated sedimentation rate and temperature, a normal white blood count and a serum transaminase level of 54. In another

TABLE 1

PATIENTS WHO DID NOT HAVE A CLINICALLY PROVEN MYOCARDIAL INFARCTION

Group II. Equivocal ECG Findings and/or Atypical History:										
Patient	*Age*	*Sex*	*Temp.*	*Number Blood Samples*	*ESR*	*Transaminase*	*CRP*	*WBC*	*ECG*	*Remarks*
					(- - - - Maximum Level - - - - -)					
1. C.B.	53	M	97.4	7	0	22	4+	11,300	Ischemia	Perineal abscess, persistent pain.
2. N.D.	72	M	100.6	5	32	42	3+	11,900	Ischemia	Persistent pain.
3. M.I.	55	F	99.0	6	13	26	0	17,000	Old infarction	Persistent pain.
4. J.R.	56	M	98.6	4	29	25	3+	7,700	Ischemia	
Group III. Angina Only and Minimal ECG Findings:										
Patient	*Age*	*Sex*	*Temp.*	*Number Blood Samples*	*ESR*	*Transaminase*	*CRP*	*WBC*	*ECG*	
					(- - - - Maximum Level - - - - -)					
5. M.B.	65	M	98.2	1	22	22	0	5,750	Old infarction	
6. R.H.	55	F	100.0	1	35	12	2+	12,950	ST-T changes	
7. J.W.	56	M	98.6	1	12	21	0	11,050	ST-T changes	

patient (B. S.) the C-reactive protein was the only abnormality noted in the studies done 8 hours prior to the onset of an infarction and several hours after an angina attack.

The erythrocyte sedimentation rate was increased in two patients in both Group II and Group III (Table 1). The white blood cell count was higher than normal in three patients in Group II, and two in Group III. The C-reactive protein was absent in the serum of only one patient in Group II, and in two of the three patients in Group III.

Of all the patients in these latter two groups, the serum glutamic oxaloacetic transaminase level was elevated in only one (N. D.) and this level was only 42 units.

Case Report

B.S., a 70 year old white physician developed substernal aching while driving his automobile on an extended trip. This radiated to the shoulder and to the medial aspect of both arms and lasted about 90 minutes. He gave a history of increasing frequency of angina pectoris beginning nine years before.

On admission to the hospital his blood pressure was 140/80; the heart and lungs were normal. The clinical impression of three observers was coronary insufficiency. An electrocardiogram was only slightly abnormal.

The following day, 8 hours prior to the recurrence of pain, erythrocyte sedimentation rate, transaminase, and white blood count were all normal. Shortly before midnight he developed severe substernal pain with radiation to the forearm which lasted over 24 hours. An electrocardiogram at this time showed an acute posterolateral myocardial infarction. Serum transaminase level 21 hours later was elevated, as was the white blood count. The erythrocyte sedimentation rate was five.

He had no further complaints but had a slight elevation of the temperature and pulse and mild hypotension for the last few days of his life. He died seven and a half days after the outset of the severe pain.

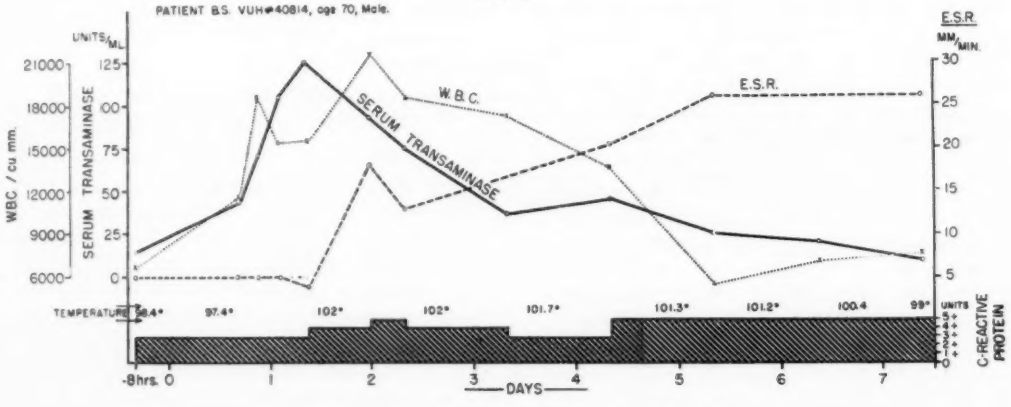
At autopsy, examination of the heart revealed a thrombosis in the lumen of the right main coronary artery, approximately 1 cm. from its origin, and a large myocardial infarction. There was no other evidence of acute tissue damage although the lungs were edematous.

We were fortunate enough to have a control blood study on this patient eight hours prior to the presumed onset of his myocardial infarction. At that time, C-reactive protein was present and all other studies, including the body temperature, were normal. The serum transaminase level was abnormal at sixteen and a half hours after the infarction as was the white blood count. It was normal at 80 hours. The erythrocyte sedimentation rate rose in the 48 hour specimen. The transaminase level rose again on the fifth day. (These findings are plotted in figure 2).

Discussion

A definitive diagnosis of myocardial infarction by electrocardiographic criteria is often beset by serious handicaps and, in some instances, is actually impossible. Thus, in the presence of a left bundle branch block or a Wolf-Parkinson-White conduction defect, a fresh myocardial infarction is seldom diagnosed by electrocardiogram. In a similar manner, significant alterations in the electrocardiogram are frequently undetectable when superimposed upon a tracing which has been strikingly altered by multiple previous infarc-

FIG. 2



RESPONSE TO MYOCARDIAL INFARCTION

tions. Again, the clinical situation is frequently encountered in which the electrocardiogram is markedly abnormal, but it does not present all of the criteria necessary for the electrical diagnosis of acute necrosis of myocardial tissue. Finally, there may be no detectable abnormality early, and sometimes even late in the course of a proven myocardial infarction.

It is largely a result of these deficiencies in the electrocardiogram that studies on the patient's blood have been made, primarily for the purpose of presenting corroborative evidence of myocardial necrosis.

One of the earliest blood studies to be correlated with the presence or absence of an acute myocardial infarction was the erythrocyte sedimentation rate. Rabinowitz, Shookhoff and Douglas[4] first showed the value of the sedimentation rate in this situation in 1931. Shillito[5] found it increased in 98 per cent of his cases. However, a number of different factors influence the fall of red blood cells, often making the results of the sedimentation rate difficult to interpret. Thus, in congestive heart failure, with passive hepatic congestion, fibrinogen is decreased and the sedimentation rate is frequently normal even if a necrotic process is present in the body. The sedimentation rate may remain elevated long after some acute infectious diseases have subsided due to the fibrinogen elevation which returns to normal very slowly. In addition, fever *per se* is often attended by an increase in the sedimentation rate.

The elevated sedimentation rate is generally the last of the commonly employed tests to appear and the longest to persist in acute myocardial infarction. In a series of 100 patients, Plotz[6] concluded that a sedimentation rate taken within the first day after a myocardial infarction would be of little value for comparison with future determinations. He also showed that an elevated sedimentation rate found between 24 and 48 hours was of great diagnostic importance, but that a negative one had little significance, and that between 48 and 72 hours nearly every rate destined to become rapid would do so. However, in some cases, the rate did not become elevated for four to seven days after the beginning of an attack.

In our series, the sedimentation rate became rapid in all but one of 11 proven infarctions. However, it was also abnormally elevated in two of the four patients with equivocal electrocardiographic findings and in two of the three patients with angina and minimal alterations in the electrocardiogram. Although in two patients the sedimentation rate was elevated within four hours after the onset of pain, in general, our data lends support to the conclusions noted by Plotz.

The C-reactive protein has been shown by Abernathy and Avery[7] to be an abnormal constituent of human serum and in all probability it is an alpha globulin produced by the body in response to an inflammatory reaction. It forms a precipitate with the polysaccharide of the pneumococcus, and small quantities are determined by a precipitation test employing a specific antiserum from rabbits hyperimmunized with purified C-reactive protein. This is measured in a capillary tube and each millimeter is considered one-plus. A one-plus reading is regarded as a sensitive indicator of an inflammatory process. It has been employed frequently as an index of rheumatic activity.[8]

Kroop and Shackman[9] found positive values as high as three-plus in the series of six patients having myocardial infarction and negative ones in six patients having coronary insufficiency. It was three-plus in the serum of a single additional patient who had "coronary insufficiency with myocardial necrosis." In a preliminary report, they suggested that the C-reactive protein might be a sensitive indicator of myocardial necrosis and inflammation. Elster, et al[10] recently concluded that the C-reactive protein level correlated roughly with the degree and persistence of fever, the white blood count and elevation of the sedimentation rate in patients who had myocardial infarction.

In the present series, there was a good correlation of the absence of C-reactive protein with a minimal or absent temperature elevation and the absence of an increased erythrocyte sedimentation rate. However, there were a few "false positives" in Groups II and III, indicating the extreme sensitivity of this test.

The fairly consistent findings of an elevated white blood cell count has been suggested as an indication of myocardial necrosis. However, this indicator is not always positive and in addition is frequently falsely positive.

It is frequently elevated in angina probably as an indication of stress. The white blood count of 17,000 in one of the patients in Group II illustrates the fact that the magnitude of the elevation is not always a sign to be related inversely to a good prognosis.

Fever is another sign which is commonly employed to indicate the presence or absence of myocardial necrosis. The absence of fever correlated in every case with the absence of necrosis. However, this finding is not axiomatic for it may be only an indication that the amount of necrosis present is relatively small.

Meyers[11] and Gilchrist[12] have applied the determination of plasma fibrinogen levels in their clinical studies of myocardial infarction. It had been shown that the normal production of six grams of fibrinogen per day in the healthy adult is greatly increased by the presence of inflammation which, with injury, is the most powerful stimulus to fibrinogen production. Gilchrist showed that 31 of 32 cases of myocardial infarction studied during the first few days, developed an abnormally high fibrinogen level. In their series, the fibrinogen level was abnormally elevated in some cases first as early as 10 hours after a myocardial infarction. Others were still normal after three days. The maximum levels were obtained about a week after the acute episode. There was a gross correlation with changes in the erythrocyte sedimentation rate. The more severe cases seemed to be associated with the greatest rise and, in some cases, abnormal levels were present three months after the acute incident. The levels were increased by moderate dosage and decreased by heavy dosage of dicumarol. This factor in addition to the technical difficulties of the procedure make this determination a less practical one in acute myocardial infarction.

Beaumont, et al,[13] employing the heparin tolerance test have demonstrated a period of hypercoagulability, often extreme, lasting from 24 to 48 hours after infarction, a spontaneous hypocoagulability from the second or third to the eighth to fifteenth post days after infarction, and a late period of hypocoagulability lasting weeks to months afterwards. However, emotional factors, infections and many other biological phenomena may affect blood coagulability.

It has also been shown that serum phospholipids, total lipids, and total cholesterol all rise in the first week of an acute myocardial infarction.[14] Recently, Vallee[15] studied serum copper values in patients who had myocardial infarction and in those who had angina pectoris. From one to three days after myocardial infarction a rise was demonstrated which reached its maximum between 5 and 11 days and steadily declined to normal over the next several days. There was no rise in the serum of patients who had angina. It is of interest that the serum copper is present in the form of ceruloplasmin, a protein complex which has been demonstrated to have enzymatic activity. Hypercupremia occurs in a multiplicity of abnormal clinical states, but the time course after a myocardial infarction may be significant. It is not known if the rise is a consequence of local tissue damage or is a secondary tissue response.[15, 16]

Recent studies have also revealed an early increase in the beta globulin and later an elevation of the alpha globulin in the serum after myocardial infarction.[17] Erlsbacher and Popp[18] investigated the changes in the serum iron level in 50 patients who had sustained recent myocardial infarctions. They found a distinct elevation in 38 during the first and second week and in 4 of the group during the third week. Two patients exhibited a permanent reduction in the serum iron level and six patients had no change at all. Preliminary studies seem to indicate that there is an abnormally low serum iron level initially (48 hours after the infarction). The levels seemed to be either normal or low for several weeks after the infarction. Although such factors as increased vagal tone, tissue asphyxia, hormonal influences, elevations of beta globulin and liberation of myoglobulin were invoked as possible theories to explain these alterations, these changes are as yet not satisfactorily understood.

Fever, leukocytosis, an elevated erythrocyte sedimentation rate and plasma fibrinogen levels, the presence of C-reactive protein, as well as alterations in blood coagulability, serum lipids, globulin, copper and iron are all nonspecific indications of an inflammatory process. They vary in their sensitiveness, and as a result of their nonspecificity all may be false indicators of myocardial necrosis if necrosis exists elsewhere in the body.

Serum Glutamic Oxaloacetic Transaminase (SGOT): Glutamic oxaloacetic transaminase is widely distributed in body tissues but is most heavily concentrated in cardiac muscle.[19] The study of serum levels of GOT following myocardial infarction[3, 20, 24] is a more direct approach toward evaluation of muscle necrosis than are any of the foregoing procedures. Consistent rises in serum transaminase levels have been demonstrated after myocardial infarction. Recently it has been shown in dogs, in which infarctions had been produced experimentally, that this rise is associated with a corresponding decrease in the transaminase concentration of the infarcted area.[21] Such studies have been made feasible through recent improvements in methodology.

Because glutamic oxaloacetic transaminase is widely distributed, one might expect serum levels to be above normal in conditions characterized by damage to tissues other than cardiac muscle.

Kattus[24] and Steinberg and Ostrow[20] have observed mild elevations after abdominal surgery. Wroblewski and LaDue[23] have noted extremely high levels in some instances of liver disease. Kattus believes that, in general, such levels are elevated for a longer period of time than are the levels of myocardial infarction, and that serial determinations will thus distinguish liver disease from myocardial infarction. Normal levels have been observed in numerous other conditions such as congestive heart failure, pneumothorax, acute and chronic infections, and uremia. Normal values have been reported in some cases of pulmonary infarction.[3, 20] Experimental infarction of the bowel in dogs,[20] and ligation of renal, splenic, mesenteric or pulmonary arteries also produced transient rises.

Elevated serum transaminase levels were noted by Steinberg and Ostrow in 22 of 24 patients who had acute myocardial infarctions. The present series indicates a consistent rise when samples are taken within 48 hours after the onset of pain. It has been suggested from graded degrees of myocardial infarction produced experimentally in dogs, that the height of the rise in transaminase is roughly proportional to the size of the infarcted area with elevations rising higher and lasting longer in the more extensive infarctions. The enzyme is very stable and, as yet, no specific mechanism has been found to explain its efficient removal within a few days after the infarction. It is conceivable that shock itself might delay this mechanism in which case the height of the rise would be unrelated to the size of the infarct.

It is hoped that myocardial insufficiency without actual tissue necrosis is not attended by an elevation in the level of serum glutamic oxaloacetic transaminase. Studies by others[3, 20] as well as the present series suggest this negative relationship. Very small myocardial infarctions produced in dogs were associated with no increase in transaminase. It seems that the complete absence of necrotic tissue will not be attended by an elevation of serum transaminase.

In our experience, the C-reactive protein method seems to be a little too sensitive for the differentiation of chest pain due to angina from that due to myocardial infarction. Erythrocyte sedimentation rates, white blood counts, rises in body temperature, fibrinogen levels as well as serum lipid or ceruloplasmin elevation and coagulation studies show a good correlation but do not represent a specific approach to myocardial necrosis which transaminase levels may afford.

Finally, it should be mentioned that although preliminary studies reveal that serum adenosine triphosphatase and serum lipoprotein lipase levels are not elevated, it is quite possible that further study of enzyme assays (e.g. lactic dehydrogenase) will reveal even more sensitive and specific indications of myocardial necrosis than that shown by glutamic oxaloacetic transaminase.

Summary

Eighty-four blood specimens were studied on 18 patients who were admitted to the hospital with chest pain suggesting angina or myocardial infarction. Erythrocyte sedimentation rates, white blood counts, C-reactive protein levels and glutamic oxaloacetic transaminase levels were performed, and correlated with clinical findings including the electrocardiograms.

Of the 11 patients who had proven myocardial infarction, (Group I), the serum transaminase level was elevated in all 10 who were studied during the first three days. It was elevated in only one of the seven patients who did not have a proven infarction (Groups II and III). The average time for

the peak level of transaminase elevation was one and a half days after the onset of chest pain; this level was usually normal by the fourth day after the onset of pain. C-reactive protein was present in the serum of all of the 10 patients studied in the first group and in 5 of the patients in Groups II and III.

These and other blood analyses which have been studied by others as aids in the detection of myocardial infarction are discussed.

It is concluded that serum transaminase levels are the most specific and most accurate clinical blood examination to detect myocardial infarctions. Serial determinations are often necessary.

This determination should be especially helpful in those clinical situations in which the electrocardiogram has little value in eliciting an acute myocardial alteration.

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Clinical Evaluation of Serum Transaminase Levels in Myocardial Infarction*

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A new test which aids in the diagnosis of recent myocardial infarction has been applied to a study of a large number of patients. It may prove to be of diagnostic help.

THIS STUDY was undertaken to evaluate the determination of serum transaminase as an ancillary procedure in the diagnosis of myocardial infarction. Widely distributed in animal tissues, glutamic oxaloacetic transaminase is most highly concentrated in the heart muscle.[1] The properties of serum transaminase have been studied by LaDue and associates,[2, 3] who found elevated levels in myocardial infarction.

Source and Method

Transaminase determinations were evaluated under circumstances similar to those in daily practice. Patients were selected by the ward resident or by physicians in private practice. Some were included because of clinical entities that might elevate the serum transaminase level. Approximately 75 per cent of the 124 patients in this series represented admissions to the Louisiana State University Medical Service of the Charity Hospital at New Orleans, and the remaining 25 per cent came from various other sources. Distribution by age, sex, and color is shown in table 1; no relationship to these factors is evident. Thirty-five patients with previously established diagnoses other than recent myocardial infarction or liver disease served as the control group (Table 2). Of the remaining 89, 36 had clinical and electrocardiographic evidence of myocardial infarction, 45 had suspected myocardial infarction not verified by electrocardiograms, 4 had electrocardiographic changes (left bundle branch block, complete heart block) of conduction defects but no definite evidence of myocardial infarction, and 4 had a diagnosis of acute myocarditis of varied etiology (idiopathic, diphtheritic, Fiedler's). The spectrophotometric method of serum transaminase determinations was used.[4]

Results

Results are summarized in table 2. The range of transaminase levels in the control group varied from six to 40 units, the mean being 16.2 units. Values exceeding 50 units were considered to be elevated, this being the lowest level observed in the group with clinical and electrocardiographic manifestations of myocardial infarction. Thirty-five of the 36 patients in this particular group had transaminase levels above 50 units, varying from 66 to 266 units. They became increased as early as four hours and as late as four days following onset of pain, and approximately 50 per cent were elevated in this group after five days. Twelve died, but postmortem examinations were obtained in only five of these, all of whom exhibited gross and microscopic evidence of a recent myocardial infarction. There was one patient with both clinical and electrocardiographic evidence of a recent myocardial infarction in whom repeated serum transaminase determinations were within the range of the normal group, the maximal level being 40 units. The first specimen was hemolyzed and was unsatisfactory.

All 45 patients with suspected myocardial infarction unconfirmed by electrocardiograms had serum transaminase levels under 50 units, varying from 10 to 48 units. None of these patients died.

Four patients with electrocardiographic changes indicating the presence of a conduction defect, but without definite evidence of

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TABLE 1

DISTRIBUTION BY AGE, SEX, AND COLOR AMONG 124 PATIENTS IN WHOM SERUM TRANSAMINASE WAS DETERMINED

	Sex		Color		Age		Total
	M	F	W	C	Mean (Yrs.)	Range	
I. Control	18	17	33	2	42	12-69	35
II. Clinical and ECG evidence of myocardial infarction	27	9	32	4	58	42-84	36
III. Suspected myocardial infarction unverified by ECG	32	13	36	9	58	39-81	45
IV. ECG changes suggestive of conduction defects	3	1	3	1	66	57-74	4
V. Diagnosis of myocarditis of varied etiology	3	1	3	1	36	21-43	4
Total	83	41	107	17	53	12-84	124

TABLE 2

TRANSAMINASE LEVELS IN 124 PATIENTS

	Number Patients	Per Cent Above 50 Units	Range (Units)	Mean (Units)	Standard Deviation (s)
I. Control	35	0	6-40	16.2	8.5
II. Clinical and ECG evidence of myocardial infarction	36	97.2	40-266	92.6	41.0
III. Suspected myocardial infarction unverified by ECG	45	0	10-50	28.4	11.4
IV. ECG changes suggestive of conduction defects	4	100.0	72-90	79.5	7.7
V. Diagnosis of myocarditis of varied etiology	4	50.0	10-60	38.0	25.9

myocardial infarction, were noted to have a serum transaminase level above 50 units (Table 2). Two of these had complete heart block but no clinical history suggestive of recent myocardial infarction. Postmortem examination of one with complete heart block revealed no gross or microscopic changes of myocardial infarction. Two patients had left bundle branch block, both of whom had clinical manifestations of myocardial infarction.

Of the remaining four patients in the series with a diagnosis of acute myocarditis of varied etiology, only two had serum transaminase levels above 50 units. Postmortem examination in one instance revealed extensive muscular degeneration consistent with myocarditis. The coronary arteries were patent.

Comment. It is interesting that the difference between the means of the control group and the group with clinical and electrocardiographic evidence of myocardial infarction was statistically significant ($P<.001$). These observations would seem to suggest a correlation between serum transaminase level and electrocardiographic findings in recent myocardial infarction and to indicate the usefulness of this laboratory procedure in the diagnosis of myocardial infarction. There is a definite need for additional investigation of serum transaminase in patients with conduction defects, particularly complete heart block and left bundle branch block. It is in this group that serum transaminase determinations may prove to be most valuable.

Summary and Conclusions

Serum transaminase levels were studied in 124 patients. These values were increased in 35 of 36 patients with clinical and electrocardiographic evidence of recent myocardial infarction but were normal in 45 out of 49 patients with no electrocardiographic evidence of recent myocardial infarction. The four patients in this latter group with elevated transaminase levels had conduction defects. Two of four patients with acute myocarditis had an elevated serum transaminase level. This procedure appears to be of value in the diagnosis of recent myocardial infarction, but further study is indicated, particularly in patients with conduction defects.

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Abdominal Trauma Requiring Surgery*

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The causes of trauma to the abdomen in this age of machines are many. Injury to viscera must always be in the doctor's mind even though the extremities or the head may be the more obvious sites of injury.

Introduction

IN SPEAKING to the general practitioner I am aware that we as surgeons are talking to the most alert group in medicine. We also know that you are the ones who see the most people with the greatest variety of disease. Your knowledge and ingenuity must of necessity be vast. You are the ones who frequently determine how soon many of these patients are to get well. I recognize the wide field of your practice and responsibility, and sympathize with you in your work. You weed out the wheat from the chaff; you see the sick and injured from the cradle to the grave. You are a great group of friends to have and with whom to work. We as surgeons stand ready at all times to be of assistance.

Causative Agents

In talking with you about trauma to the abdomen which requires surgery, I must remind you that there are many more mechanical devices now than a few years ago, and that injuries occur more frequently. Not too many years ago the horse and buggy, wagon, sawmill, cotton gin, the steamboat and trains caused many of the injuries we will talk about. Today there are many more mechanical things, and many more people using them, such as,—the tractor, automobile, bus, streamline trains, aeroplanes, factories with complicated machinery and many other mechanical devices. The atomic bomb and now the hydrogen bomb has been added to the list. All these can and do produce trauma. Every entrance into the abdomen produces some trauma since cutting into the peritoneum, actually also is surgical trauma.

The agents carrying trauma may be classified as direct and indirect. The direct may be divided into penetrating and nonpenetrating. Since this is to be a practical presentation of the subject, and not a didactic one with a voluminous bibliography, we will review our experiences and those of others with the hope it be profitable to all. We have gained much from the review we have made of our past work.

Diagnosis

Diagnosis is the most important phase of the subject. In this day of many injuries, it is generally a layman who first sees or picks up the injured person. Next, it is the ambulance driver who must be taught how to handle the injured in order to maintain a clear airway and not to increase the difficulty. The general practitioners as a group see more of these people than any others in the medical profession.

When the patient is presented to us with the history of injury, we must always find out as much as possible about how it happened, either from the patient or from someone who saw the accident. Of course, penetrating injuries are self-evident, and inspection locates the portal of entry, which requires meticulous care and treatment. In nonpenetrating injuries one is confronted with direct and indirect types of trauma and one must look carefully for the signs and symptoms of the injury to the contents of the abdomen as well as to the abdominal walls, roof and floor. We know, but should be reminded, that the abdomen has a muscular wall anteriorly, muscular and bony wall posteriorly in which the kidneys, ureters and adrenals are closely allied with the abdominal cavity. Above, the roof is formed by the diaphragm, and the floor below by the pelvis and pelvic floor muscles. Injuries to these adjacent parts are of vital importance since they affect the contents of the abdominal cavity. We must remember always that, while the patient may have a fractured humerus and/or femur which produces severe shock, at the same time all the shock

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may not be due to those injuries alone. A ruptured spleen, liver, kidney or hollow viscus may be associated with this injury. The symptoms may be masked by the early noticeable injury to the extremity.

Careful observation, examination, and inspection of the patient must be carried out, even though we may feel that a single diagnosis should explain most diseases. Yet this is not true with injuries. Regardless of the injury, shock and/or hemorrhage should be combatted while observation is being carried out. It should be sufficient to say that blood, fluids, opiates (except when there are certain associated head and chest injuries), and a clear airway for respiration are indicated first. While this is being done, a careful survey and examination may be done to determine all the injuries to the patient.

Case Material

The diagnosis may best be illustrated by the following cases.

Case 1. This was a typical instance of a patient with a ruptured left diaphragm, and with the stomach and colon in the left chest, complaining of inability to swallow, air hunger, some shock and no visible evidence of trauma, which was caused by a head-on collision while riding in the right side of the cab of a truck.

Case 2. This was a young man, 22 years of age, who, at the age of 7, was in a school-bus wreck, and was treated for three weeks at that time in a small rural hospital for pneumonia of the left side which he eventually overcame. We believe now that he did not have pneumonia but did have a rupture of his diaphragm with his stomach, colon and small bowel in the left chest which disabled him for 15 years until recognized by us. All that was needed was an x-ray examination of the chest, and now since repair of his hernia he and his family are well and happy.

Case 3. This 8 year old boy fell from a tractor and was run over in the soft ground by a rubber tired wheel. He was in shock when we saw him, with air hunger and inability to get a deep breath. His right diaphragm was elevated and stationery, his abdomen was rigid, caused by rupture of the right lobe of the liver next to the diaphragm. This was repaired by the use of Gelfoam and deep sutures in the liver with a flat, blunt needle using No. 3 chromic catgut doubled. Fine cotton and silk have no place in such a repair because it cuts out badly in the liver tissue.

Case 4. This boy, aged 9, fell from a wagon loaded with corn; the rear wheel passed over him, on muddy ground. The country general practitioner could not rally him completely from shock and, though improved when we saw him, his abdominal pain, peritoneal reflex and rigidity, low blood pressure, rapid pulse, fever, gaseous distension, decreasing hematocrit and shifting fluid level in the abdominal cavity pointed toward a ruptured solid viscus.

Case 5. A man, working on the construction of a house, fell from the second to the first floor, the abdomen striking a joist, as his body fell across it. He was not in a state of shock when he was first brought in, but shortly he became quite ill, with a rapid pulse, drop in blood pressure and a cold clammy skin. The abdomen became rigid; pain was severe. X-ray studies revealed air under the diaphragm. At operation a ruptured duodenum was found compressed against the body of the vertebra.

Case 6. In a taxicab collision, a young lady suffered a fracture of the jaw, right radius and clavicle, and multiple contusions, some of which were to the abdomen. After being brought out of shock, she began to have abdominal discomfort, nausea, vomiting, excruciating pain, along with rigidity. Upon exploration the symptoms were proven to be due to a ruptured pancreas which was sutured and drained. (In my opinion, nothing causes such severe excoriation of the skin as do draining pancreatic juices. Aluminum powder applied to the well cleansed skin will protect it and prevent excoriation.)

Case 7. This young girl was swinging on a porch swing when the chain broke and she was thrown out in the yard. Shock with a thready pulse, and abdominal pain followed by distension developed. The cause of her disability was a compression fracture of the body of the twelfth dorsal vertebra masking signs and symptoms of an intra-abdominal lesion. Other viscera may be ruptured or injured by trauma to the abdomen.

A ruptured kidney is usually produced by a direct blow in the lumbar or flank region on either side. It may or may not produce a severe hemorrhage but is very shocking to the patient and requires immediate and careful treatment. A ruptured bladder is usually produced by direct violence and often is torn by a fracture of the pelvic bones. Pressure on the abdomen, even if not directly over the bladder may cause it to rupture when it is filled. It is very often torn by penetrating objects as in wrecks and the like.

Rupture of an ovarian cyst with resulting hematoperitoneum happened to me once while carefully doing a bimanual examination, followed in a few hours by the usual signs of shock and hemorrhage requiring surgery. We also had a patient to whom this happened during intercourse with her husband, followed by hematoperitoneum. We have seen rupture of the sigmoid caused by the trauma of introduction of a foreign body into the rectum perforating the sigmoid colon and producing peritonitis.

A hematoma of the abdominal wall has been encountered in a sawmill worker who was hit above the pubis by a cant-hook handle. He had signs of peritoneal irritation, and pain with shock and evidence of increase in size of

the lower abdomen. Exploration revealed the lesion to be extraperitoneal. Surgical trauma is done every time we invade the peritoneal cavity but we must lessen the amount as much as possible. We have seen the mesentery of the sigmoid colon torn by too vigorous packing done against a distended bowel, or hemorrhage into the peritoneal cavity from failure to secure a blood vessel of the ovarian pedicle, or a hematoma of the broad ligament extending up the retroperitoneal space. These all produce mild to severe forms of shock, nausea, vomiting and ileus and should be recognized postoperatively. Ureters have been tied or severed in the course of pelvic surgery followed by a rather stormy convalescense. Ligation of the common duct is another example of surgical trauma.

Treatment

When we treat patients with abdominal trauma our main objective is to save the life of the patient. We must arrest hemorrhage, but at the same time maintain a clear airway with adequate respiratory exchange. Since shock is prominently associated with these abdominal injuries, we must turn our attention to this important symptom and treat it vigorously in the usual way with drugs (preferably intravenously), drips, blood, Trendelenburg position, clear airway to prevent anoxia, oxygen intranasally, if needed, and careful observation,—pulse, blood pressure and hematocrit determinations. When shock is overcome, hemorrhage is arrested, and respiratory exchange is satisfactory with no oxygen deficiency, we are ready to turn to definitive treatment which must include prevention of infection locally and systemically. We must remember that we are treating *a patient* with abdominal trauma, not just abdominal trauma. Definitive treatment consists of saving the traumatized part and restoring it to its normal function and appearance if possible.

Penetrating wounds should be followed down to the abdominal cavity by operation, never probing the point of entry. Ample blood must always be available, for large vessels may be severed, torn or penetrated. Careful, rapid, but unhurried repair is in order once the patient is in condition to begin definitive treatment. With present day anesthesia this is more easily done than heretofore.

Continuous gastric suction is indicated in all patients having abdominal injuries in which the gastrointestinal tract is opened, as well as in other injuries which produce ileus. The chlorides and potassium must be replaced when removed by suction, but I caution against the overenthusiastic use of intravenous fluids to the point of water-logging the patient. From here on the patient should be treated as any other abdominal operative case.

Conclusion

(1) The patient with abdominal trauma is most frequently seen first by the general practitioner.

(2) The present mechanical age permits of more trauma to more people than heretofore.

(3) Penetrating wounds are generally self-evident but may not always perforate the abdominal organs.

(4) Ruptured or perforated organs within the abdomen produce shock which cannot immediately be differentiated from shock caused by the complicating fractured femur, head injuries or other injuries.

(5) Shock and hemorrhage must be overcome before definitive treatment is begun.

(6) Multiple injuries must be studied carefully to rule out the hidden abdominal trauma which is evident later.

(7) Illustrations of the various types of the most frequently encountered injuries have been presented.

(8) Details of treatment have been omitted for brevity.

Discussion (Abstract)

Dr. Vencel W. Hollo, St. Louis, Mo. Drs. Long and Dees have given an excellent summary of an extensive subject in the discussion of trauma of the abdomen.

The only comments I might make is to emphasize that a careful history and physical examination are very important in evaluating the injuries sustained to the abdominal wall and its contents, in making a differential diagnosis. One must also keep in mind that an individual may be in an accident and receive an injury and at the same time a pathologic process may have been present in the abdominal cavity at the time of the accident. I have two such cases in mind.

One case was that of a patient approximately 60 years of age who, in an automobile accident, suffering injury to the right lower chest and upper abdominal wall, and right side when he was struck by the steering wheel. The patient had excruciating pain, and marked tenderness, localized in the right upper quadrant. Pain also radiated to the posterior walls of the chest.

He had slight elevation of temperature and leukocytosis, which occurs in tissue trauma. However, on close observation, the examining doctor detected some slight icterus of the cornea. The patient had a plain film made of the abdomen which revealed multiple calculi in the right upper quadrant. The preoperative diagnosis was cholecystitis and partial obstruction of the common duct. At operation the diagnosis was confirmed. Cholecystectomy was done, a stone was removed from the common duct and the patient had an uneventful recovery.

The second case was that of a 36 year old male who gave a history of having lifted a heavy object, and approximately one hour later suffering excruciating back pain which doubled him up. He was taken to the hospital on a stretcher.

Close questioning of the patient revealed that he did hurt his back when lifting an object while working, and that an hour later he suffered excruciating pain. However, on further question, the patient's pain was found to radiate to the right testicle and he also had dysuria and polyuria. There was also spasm and tenderness in the lumbar region.

Cystoscopic examination eight hours after the trauma revealed no evidence of ureteral calculi. Retrograde pyelograms were normal.

On the following morning, the patient was examined and the urinalysis was negative. I instructed him to strain his urine so that he might retrieve any foreign objects passed. On the following day he brought in two renal calculi. Had this patient not been seen again and been advised to strain his urine, I am of the opinion the diagnosis in this case would have been lumbodorsal strain. He made a spontaneous recovery.

These two cases illustrate that whenever a patient is involved in an accident with trauma to the abdominal wall, whether penetrating, direct, or indirect, one should always keep in mind that other pathologic diseases may be in process. Therefore, frequent and repeated examinations of the patient are necessary and a very careful history should be obtained and physical examination should be thorough in order to arrive at the proper diagnosis.

A Biochemical Test for Chorionic Gonadotrophin in the Urine and Its Value as an Aid in the Diagnosis of Pregnancy and Malignancy*

T. C. TERRELL, M.D., and H. H. BEARD, Ph.D.,† *Fort Worth, Tex.*

The authors report preliminary studies in the use of the excretion of chorionic gonadotrophin as a diagnostic and prognostic aid in cases of malignancy.

TESTS FOR PREGNANCY, the well known biologic test for chorionic gonadotrophin in the blood and urine, are usually direct. Even though these tests are very accurate for the diagnosis of pregnancy, the results of any biologic test leave much to be desired from the quantitative biochemical point of view. Tests for malignancy on the other hand are usually indirect, and as such they will probably never find clinical acceptance since they are apt to give too many false positives. It is, therefore, evident that an accurate quantitative and highly specific biochemical test for both pregnancy and malignancy is needed.

For a number of years we have been attempting to develop such a test for chorionic gonadotrophin which can be carried out in any well equipped laboratory. We have found the results of this test to be of value as an aid in the diagnosis of pregnancy and malignancy. In both of these conditions the excretion of

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chorionic gonadotrophin is increased and we feel that by using this index it may be of value in the diagnosis of the condition.

Principle and Technic

The acetone precipitate of the urine, after removal of the solvent, is dissolved in phosphate buffer, and anthrone-sulfuric acid is added to an aliquot of the solution of the precipitate added to distilled water. The resulting color after cooling is measured in the spectrophotometer. The process is then repeated after digesting a small sample of the precipitate solution with crystalline chymotrypsin at 37° overnight. Chorionic gonadotrophin is completely digested under these conditions while other substances, such as the anterior pituitary gonadotrophins, polysaccharides, etc., which also give the anthrone reaction, are not digested. The concentration of chorionic gonadotrophin can, therefore, be calculated as the difference between the values obtained before and after digestion.

The importance of collecting an accurate 24 hour urine volume cannot be overemphasized. A small sample of urine may give a negative result. The sample must be preserved with 15 cc. of acetone or alcohol, the 24 hour volume must be recorded, and a pint of the urine sample is needed for the laboratory study.

FIG. 1

ABSORPTION SPECTRA OF GALACTOSE & "APL" (HUMAN CHORIONIC GONADOTROPHIN)

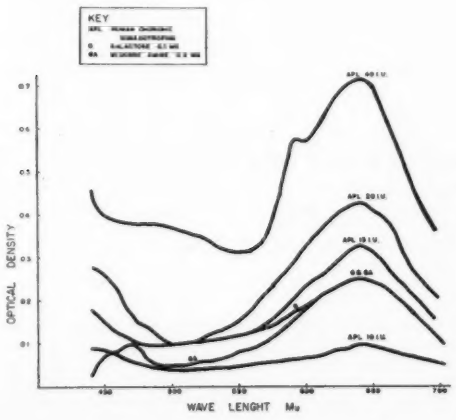
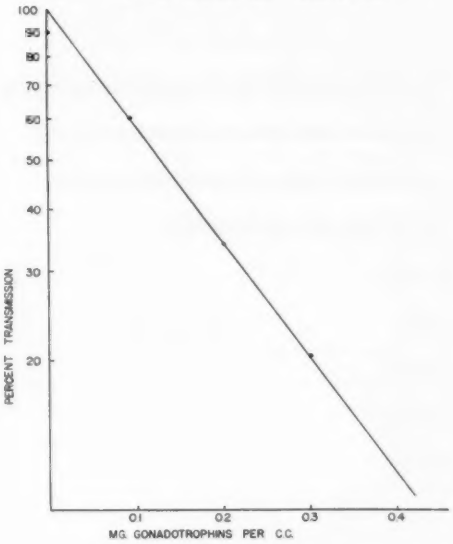


FIG. 2

GONADOTROPHINS (LH)

AYERST APL NO. 26519 65 I.U. PER MG.



Technic. 1. Add 800 cc. of acetone to 200 cc. of the urine sample in a 2000 cc. Florence flask, connect to an electric stirrer and stir for four minutes. Allow the precipitate to settle, decant, and filter through a fluted filter. Discard the filtrate, dissolve the precipitate in 40 to 200 cc. of phosphate buffer, pH 7.6, and again filter through the filter paper. Pour the filtrate in a breaker and distill off the remaining acetone in a vacuum oven at 60°C. (20-25 lb. vacuum) for 20 minutes. Cool and make up to known volume with more buffer solution.

2. Dissolve 500 mg. anthrone (Eastman) in 240 cc. of concentrated sulfuric acid (AR). Make fresh or allow to stand in ice box no longer than three days.

3. To each of six, 50 cc. Erlenmeyer flasks pipette in 5 cc. of distilled water. To flask 1 add 10 cc. of anthrone-sulfuric acid from a special burette. To flasks 2 through 6 add 0.1 or 0.2 cc. of the sample followed in each case by 10 cc. of anthrone-sulfuric acid. Shake all flasks and allow to stand at room temperature for 35 minutes.

4. With the blank tube 1 in the left hand curvette of the Coleman universal spectrophotometer adjust the galvanometer light scale to 100 per cent transmission at 640 millimicrons using filter PC-4. Then in succession place the tubes containing the samples in the right side of the curvette carrier and measure the per cent transmission. Take the average value. This is the "total gonadotrophin" (chorionic gonadotrophin, anterior pituitary gonadotrophins, polysaccharides, etc.) (TG).

FIG. 3

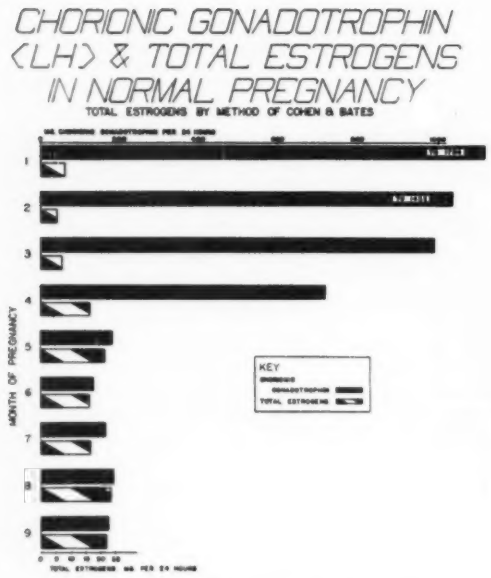
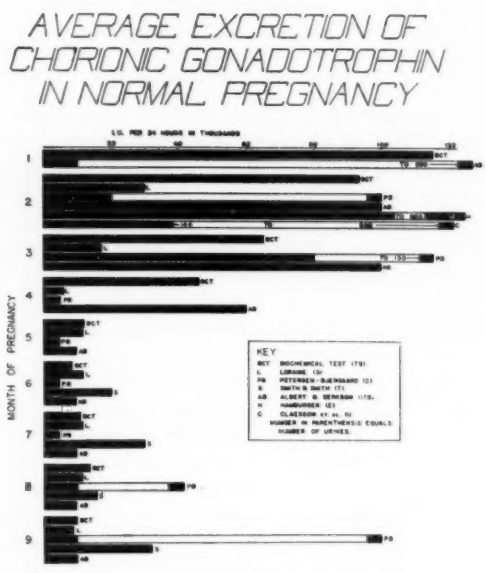


FIG. 4



5. To a 5 mg. vial of crystalline chymotrypsin add a small amount of the sample under 1 above, dissolve the enzyme, and pour the contents into a screw capped test tube, screw on cap, and incubate tube at 37°C. overnight. Using the same aliquot as in 3 above, rerun the sample. This gives the "residual gonadotrophin" (anterior pituitary gonadotrophins, polysaccharides, etc.) (RG).

Then TG — RG = CG. (mgs.).

6. Make a standard solution of chorionic gonadotrophin (APL) in distilled water (1 cc. = 1 mg. APL*) and add 0.1, 0.2, 0.3, 0.4 cc. of this solution to 4.9, 4.8, 4.7 and 4.6 cc. of distilled water. Add 10 cc. of anthrone-sulfuric acid to each flask, shake, allow to stand for 35 minutes at room temperature and read as above. From this standard curve on semilogarithmetic paper the concentration of the total and residual gonadotrophins can be determined.

7. Calculate the chorionic gonadotrophin in mg. per 24 hours. Values above 30 mg. per 24 hr. are indicative of pregnancy or malignancy.

8. Recovery of different types of gonadotrophins added to water. While the anterior pituitary gonadotrophins FSH and LH could be excreted and determined in the "residual gonadotrophin" fraction above, we have no assurance that these hormones would be present in a given sample. Nevertheless we tested the pure anterior pituitary follicle stimulating and luteinizing hormones of Armour and Company and in water solution these hormones were recovered to a 100+ per cent accuracy.

The above test serves to estimate the galactose content of the chorionic gonadotrophin. The presence of glucosamine in the hormone does not modify the results obtained with pure galactose alone (Fig. 1). The maximum absorption was at 640 mμ when 10 to 40 IU of the chorionic gonadotrophin is determined.

*Equal to 0.08 mg. chorionic gonadotrophin.

TABLE 1

CHORIONIC GONADOTROPHIN EXCRETION IN NORMAL INDIVIDUALS

Name	*CG mg./24 hrs.*	*Name*	*CG mg./24 hrs.*	*Name*	*CG mg./24 hrs.*	*Name*	*CG mg./24 hrs.*
Mrs. CM	0	Mrs. TM	16	HHB	6	WR	8
No. 7	2	No. 8	13	No. 9	3	No. 26	24
No. 86	24	No. 111	28	S	7	GW	9
LW	25	LB	12	No. 69	20	No. 13	20
No. 22	5	M	36	EAT	0	H	27
GW	29	Mrs. D	24	Miss H	1	HC	0
Mrs. C	15	Miss DE	14	Mrs. M	16	DF(1)	0
DF(2)	0	DF(3)	0	DF(4)	0	DF(5)	0
DF(6)	0	Mrs. GG	0	LB	4	IHB	10

The average excretion curve for this hormone is shown in figure 2, from which all data in this paper were obtained.

The addition of anthrone-sulfuric acid to the water sample of the hormone serves to digest the glycoprotein and the liberated galactose reacts with the anthrone at the same time to produce the characteristic blue-green color. The other substances which may be present in the urine either are not precipitated with acetone or are not digested with chymotrypsin and would be encountered in the residual gonadotrophin fraction. For this reason we have never used blood filtrates since here again there are too many substances that could give false positives.

Results

Normal Individuals. Results obtained are listed in table 1. Since only a few of these had above 30 mg. of chorionic gonadotrophin (APL) per 24 hours we have tentatively concluded that a titer above this indicates pregnancy or malignancy while one below is probably due to experimental error of the method.

Normal Pregnancy. Results in the urines of 78 normal young pregnant women are shown in figure 3. Total estrogen determinations

TABLE 2

CHORIONIC GONADOTROPHIN AND TOTAL ESTROGEN EXCRETION IN OTHER CONDITIONS

Case Number	*Name*	*Diagnosis and Remarks*	*CG* (mg./24 hrs.)*	*TE**
1	Mrs. W.A.G.	Acute yellow atrophy of liver (died 4 days later)	258	
2	Mrs. J.C.McM.	Cirrhosis of liver	21	
3	Mr. O.L.G.	Cirrhosis of liver	556	112
		(Treatment for 1 week)	13	6
4	Miss F.T.	Hypertension and cholelithiasis	10	
5	Mrs. D.B.	Cholelithiasis, cholecystitis and osteoarthritis	0	0
6	Mr. W.R.	Arteriosclerotic heart disease and treated lues	20	18
7	Mrs. R.H.	Arteriosclerotic heart disease with congestive failure	2	2
8	Mrs. D.E.P.	Chronic bronchitis and hypertension	0	
9	Mrs. G.McD.	Hypertensive heart disease and uncontrolled diabetes	472	
		(Test due to sugar in urine. Died 4 mo. later)		
10	Mrs. V.C.	Generalized arteriosclerosis and virus infection	18	4
11	Mr. E.S.	Diabetes, controlled	31	
12	Mr. C.W.P.Jr.	Duodenal ulcer and hemorrhage	0	
13	Dr. E.R.S.	Healed gastric ulcer. No active lesions	0	0
14	Mrs. L.	Gastric ulcer and anemia	22	
15	Mrs. I.M.	Fatigue	4	
16	Mrs. M.S.	Schizophrenia	7	
17	Mrs. P.C.C.	Severe anxiety state	27	
18	Mrs. D.N.	Malnutrition and adrenal deficiency	35	5
19	Mr. O.F.	Acromegaly	411	
20	Mr. C.C.G.	Acute pancreatitis	12	
21	Mrs. E.T.C.	Chronic tuberculosis	17	
22	Mrs. M.W.	Tuberculosis, perioneal type	0	1
23	Mrs. J.L.R.	Arthritis of neck (estrogen therapy)	0	18
24	Mr. R.H.M.	Arthritis	25	4
25	Mr. H.W.	Otitis media	0	0
26	Mrs. N.V.N.	Hyperhydrosis	19	3
27	Mrs. R.T.M.	Recurrent uterine bleeding (functional)	7	6
28	Mrs. V.M.R.	Endometriosis and cystic ovary—before operation,	86	
		—after operation	12	
29	Mrs. E.E.B.	Peripheral vascular dystrophy (cortisone therapy)	10	6
30	Mrs. B.	Fibrocystic disease of breast (4 wk. preoperative)	93	
		Three wk. postoperative	77	
		Six mo. postoperative	26	
31	Mrs. N.C.	Lipoma of breast	0	
32	Mrs. R.McK.	Pregnancy, about 1 mo.	205	23
33	Mrs. C.S.	Friedman positive	0	8
		Pregnancy (1 mo. later)	355	12
34	Mrs. J.N.	Hydatidiform mole, 2 mo. after removal	53	
		Hydatidiform mole, 5 mo. after removal	0	
35	Mrs. M.L.D.	Excessive bleeding. Labor induced 6 days later and hydatidiform mole passed	3944	129
		Six days after mole passed	38	
		Four wk. after mole passed	20	

*CG—Gonadotrophin; TE—Total Estrogens.

were done at the same time for comparative purposes. The results obtained in the excretion of both hormones are in line with those of other investigators in human pregnancy (Fig. 4).[35-39] From these results it is obvious that the anthrone test measures the quantitative excretion of chorionic gonadotrophin in the urine.

Other Clinical Conditions. In this group were 35 urines, two from normal pregnant women, and two from patients having hydatidiform moles. Assuming that these positive results were correct, there were 31 remaining urines. The false positive results occurred as shown in table 2, in acute yellow atrophy of liver, cirrhosis of liver, hypertensive heart disease and uncontrolled diabetes (test due to sugar), malnutrition and adrenal deficiency,

TABLE 3

CHORIONIC GONADOTROPHIN AND TOTAL ESTROGENS IN MALIGNANCY

Case Number	*Name*	*Diagnosis and Remarks*	*CG* (mg./24 hrs.)*	*TE**
1	Mr. J.T.	Melanoma of arm-metas to lymph nodes	113	18
2	Mrs. J.W.C.	Melanoma of heel, 2 x 2 cm.	0	19
3	Mr. M.B.	Melanoma of back	76	0
4	Mrs. B.J.	Melanoma of cheek, 1 x 1.5 cm.	0	3
5	Mrs. J.B.D.	Metastatic melanoma, terminal	53	21
6	Miss B.B.	Duct cell Ca. of breast, grade 3	64	0
7	Mrs. F.T.	Duct cell Ca. of breast, grade 3	85	8
8	Mrs. M.S.	Duct cell Ca. of breast, grade 3	70	5
9	Mrs. A.P.	Duct cell Ca. of breast, grade 3	108	31
10	Mrs. H.E.McV.	Adeno-Ca. of breast, grade 3, and adeno-Ca. of rectum	98	0
11	Mrs. L.F.L.	Adeno-Ca. of breast	51	36
12	Mrs. A.M.K.	Ca. of breast-metastasis to bone	244	3
13	Mrs. T.L.	Recurrent Ca. of breast	43	18
14	Mrs. K.	Ca. of breast (terminal)-metastasis to ribs and mediastinum	2416	45
15	Mrs. S.N.	Bronchogenic Ca.	163	58
16	Mr. P.K.	Ca. of esophagus, grade 3	47	13
17	Mr. T.M.	Ca. of bronchus, throat and esophagus	79	8
18	Mr. G.P.	Ca. of esophagus	151	33
19	Mrs. L.	Metastatic Ca. of lung	43	17
20	Miss D.C.	Primary bronchogenic Ca. of lung, grade 3	190	39
21	Mrs. T.H.M.	Adeno-Ca. of rectum-metastasis to lymph nodes	202	77
22	Mr. V.B.	Adeno-Ca. of sigmoid	617	34
23	Mr. R.S.	Ca. sigmoid, rapidly growing tumor	817	14
24	Mrs. H.B.	Ca. of rectum	75	14
25	Mrs. P.H.C.	Adeno-Ca. of rectum	83	23
26	Mr. P.W.	Adeno-Ca. of rectum	251	15
27	Mrs. I.C.	Adeno-papillary Ca. of rectosigmoid-metastasis to regional lymph nodes	83	11
28	Mrs. W.R.J.	Ca. uterus, metastasis to pelvis (died 1 mo. later)	113	4
29	Mrs. M.H.	Adeno-Ca. of endometrium	50	28
30	Miss M.B.	Adeno-Ca. of endometrium	270	15
31	Mrs. A.R.	Serous papillary cystadenocarcinoma of left ovary, grade 2	113	4
32	Mr. W.C.Jr.	Multiple myeloma	46	0
33	Mrs. J.L.	Multiple myeloma	40	10
34	Mr. H.H.	Malignant lymphoma	126	35
35	Mrs. B.F.	Lymphosarcoma	58	8
36	Mrs. J.T.	Adeno-Ca. of pancreas-metastasis to liver	147	32
37	Mrs. M.deL.	Ca. of pancreas	167	33
38	Mrs. W.W.W.	Ca. of liver, metastasis to brain	264	23
39	Mr. F.A.Jr.	Seminoma of testicle, removed	42	39
40	Mrs. J.H.G.	Hypernephroma, metastasis to humerus	156	23
41	Mrs. I.L.L.	Ca. of stomach, generalized carcinomatosis	288	24
42	Mr. J.H.	Neuroblastoma, generalized metas	74	36
43	Mrs. L.T.	Adeno-Ca. of neck	156	8
44	Mrs. H.C.	Ca. of cervix	31	14
45	Mrs. F.H.	Early lymphatic leukemia	139	8
46	Miss B.L.	Acute lymphatic leukemia	65	18
47	Mr. R.I.	Lymphatic leukemia	109	5
48	Mrs. A.L.McL.	Chronic lymphatic leukemia	41	1
49	Mr. D.H.	Acute lymphatic leukemia	0	11
50	Dr. J.F.W.	Myelogenous leukemia following polycythemia	74	0
51	Mr. C.S.	Myelogenous leukemia	549	35

*CG—Gonadotrophin; TE—Total Estrogens.

TABLE 4

CHORIONIC GONADOTROPHIN AND TOTAL ESTROGEN EXCRETION IN PROGNOSIS IN MALIGNANCY

Case Number	*Name*	*Date*	*Diagnosis—Treatment—Remarks*	*Date*	*CG (mg./24 hrs.)*	*TE*
1	Mrs. J.B.D. Age 56	Mar. 11, 1954	Terminal metastatic melanoma; 2000r between Mar. 29 and May 3	Mar. 11	63	21
				Mar. 29	103	40
				Apr. 26	26	5
2	Mrs. D.B. Age 27	May 7, 1954	Melanoma; 6 wks. pregnancy; melanoma removed, therapeutic abortion (2 wks. later)	May 7	122	3
				June 15	0	6
3	Mrs. A.P. Age 54	Jan. 9, 1952	Adeno-Ca. of right breast; radical mastectomy followed by x-ray therapy; died 8 mo. later	Aug. 7, 1953	108	31
4	Mrs. M.S. Age 48	July 9, 1953	Operation, duct cell Ca. of breast, grade 3, with metastasis to regional lymph nodes	June 13	70	5
				Aug. 10	49	5
				Apr. 26, 1954	36	5
				July 15, 1954	0	6
5	Mrs. T.L. Age 56	Jan. 29, 1952	Ca. of breast; mastectomy	May 4, 1954	48	13
		Mar. 5, 1954	Extensive metastatic lesions	May 20, 1954	88	38
6	Miss B.B. Age 60	Apr. 20,1954	Operation, duct cell Ca. of breast, grade 3, with metastasis to axillary lymph nodes	Apr. 4	64	0
				July 1	0	2
				Oct. 1	0	2
7	Mrs. A.M.K. Age 63	Mar. 8, 1953	Operation, Ca. of breast, with metastasis to bone; x-ray and testosterone therapy; died Oct. 1954	Feb. 17	244	46
				Feb. 20	364	65
8	Mr. P.K. Age 73	Aug. 9, 1953	Biopsy, Ca. of esophagus, grade 3; died Jan. 1954	Aug. 11	47	13
				Sept. 4	62	47
				Oct. 3	41	42
				Nov. 23	205	61
9	Mrs. R.L.T. Age 54	Aug. 8, 1948	Squamous cell Ca. of cervix, grade 3; no evidence of malignancy in 1949, 1951 and 1952	May 21, 1953	53	4
				July 28, 1953	5	3
		June 5, 1953	Metastatic mass in broad ligament removed and radon seeds implanted; died Oct. 1954	Sept. 15, 1953	95	51
				Dec. 17, 1953	101	45
10	Mrs. C.C. Age 62	Apr. 2, 1952	Squamous cell Ca. of cervix, removed	Dec. 6, 1953	0	3
11	Mrs. M.T. Age 50	1945	Cervix adeno-Ca. of cervix	Mar. 2, 1952	23	
		1946	Total hysterectomy; local treatment	Dec. 7, 1953	50	
		1947	Radium application to lesion in vault of vagina	Dec. 29, 1953	90	
		1952	No evidence of malignancy 1300 mg. hr.			
		Dec. 1953	No evidence of lesion in vagina			
12	Mr. P.H. Age 48	Oct. 23, 1953	Transurethral resection; adeno-Ca. of prostate	Nov. 27, 1953	4	
		Dec. 2, 1953	Stilbesterol therapy	July 28, 1954	32	8
		July 28, 1954	Tyvid therapy			
13	Mrs. T.H.M. Age 63	Aug. 3, 1953	Rectal bleeding for several years; abdominal perineal resection for Ca. of rectum with lymph node metastasis (adeno-Ca. of rectum). Apparently well 1 year later	Jan. 5, 1954	202	77
		Sept. 19, 1953				
14	Mr. R.S. Age 49	1952	Primary Ca. of sigmoid; operation and colostomy	May 30, 1954	617	14
		May 30, 1954	Tumor growing rapidly; died 6 wk. later			
15	Mrs. J.W. Age 48	Oct. 23, 1952	Operation for adeno-Ca. of transverse colon, grade 2	Jan. 3, 1954	0	
				Apr. 20, 1954	0	11
16	Mr. D.R.S. Age 52	Nov. 23, 1953	Operation, adeno-Ca. of rectum, grade 3	July 9, 1954	17	0
17	Mr. V.B. Age 54	Mar. 22, 1953	Left colon resection for adeno-Ca. of sigmoid, grade 3. Intestinal obstruction 2 mo. later; death in 1 wk. Autopsy, recurrent adeno-Ca.—Ca. of sigmoid	Apr. 10, 1953	100	10
				May 13, 1953	161	22
18	Mrs. G.T. Age 60	June 26, 1954	Ca. of colon, removed	July 8, 1954	0	
19	Mrs. E.P.M. Age 66	June 5, 1953	Operation—Ca. of rectum	Dec. 12, 1953	0	
20	Mrs. P.H.C. Age 56	Apr. 17, 1952	Adeno-Ca. of large intestine, grade 3, with metastasis to lymph nodes; well 2½ yr.	Sept. 11, 1953	79	
				Sept. 13, 1954	83	10
21	Mrs. D.J. Age 52	Mar. 29, 1954	Operation—adeno-Ca. of rectum, grade 3	Sept. 18, 1954	0	8
22	Miss M.B. Age 66	Aug. 1, 1951	Biopsy and curettage, adeno-Ca. of endometrium, grade 3. Radium and x-ray therapy; died carcinomatosis, primary site the uterus, 3 yr. later	May 8, 1953	106	25
				Jan. 2, 1954	270	57
23	Mrs. M.H. Age 62	Apr. 19, 1954	Panhysterectomy for adeno-Ca. of endometrium	May 14, 1954	50	28
				May 19, 1954	57	12
24	Mrs. A.R. Age 53	Sept. 3, 1953	Papillary cystadenocarcinoma of left ovary, operated	Sept. 8, 1953	147	33
				May 4, 1954	45	92
25	Mrs. W.W.W. Age 80	Aug. 10,1953	Cerebrovascular accident; lupus erythematosis; died 5 mo. later; autopsy, Ca. of liver, metastatic to brain	Sept. 10, 1953	57	
				Oct. 1, 1953	264	24
26	Mrs. V.McC. Age 53	Feb. 27, 1953	Retroperitoneal lymphosarcoma; total of 2700r given; died 18 mo. later	Jan. 10, 1954	0	1
				May 15, 1954	0	1
				Aug. 23, 1954	145	32
27	Mrs. S.N. Age 42	Aug. 25, 1953	Biopsy, bronchogenic Ca. Operation	Aug. 12, 1953	163	21
				Sept. 2, 1953	29	
28	Mr. J.M.H. Age 18	Sept. 22, 1953	Enlarged inguinal nodes. X-ray therapy; died 5 wk. later; autopsy, neuroblastoma with generalized metastases*	Sept. 22, 1953	74	36
				Oct. 5, 1953	83	86
				Oct. 7, 1953	180	93
				Oct. 9, 1953	245	121
29	Dr. J.W.	1946-1954	Myelogenous leukemia following polycythemia	Jan. 3, 1954	74	11
				Oct. 15, 1954	178	14

*The urines from the last three determinations were processed by our kaolin-alkali-milk technic. The isolated powder gave a positive anthrone, biological and Friedman test for chorionic gonadotrophin.

acromegaly, endometriosis and cystic ovary, and fibrocystic disease of the breast.

It is realized that this number of cases is inadequate, but it is obvious that false positive results may be obtained in urines from the following types of cases: Pregnancy, postpartum states, hydatidiform mole, diseases of the liver, and in any other condition where an excess of the chorionic gonadotrophin may be excreted.

Malignancy—Diagnosis. In 51 cases the excretion of chorionic gonadotrophin exceeded 30 mg./24 hr. in 94 per cent, and estrogens were high in 90 per cent, while a positive test for either the gonadotrophin or estrogens was obtained in 100 per cent of the cases (Table 3). All cases reported in this paper had a proven diagnosis of malignancy.

Malignancy—Prognosis. Twenty-nine cases are presented in this group. The data are listed in table 4. The possible absence of metastasis after operation is illustrated by the results obtained in cases 2, 4, 6, 10, 16, 18, 19 and 27 in all of which the chorionic gonadotrophin titer was zero except in cases 16 and 27. The probable presence of a metastasis was shown by the positive titers obtained in cases 1, 5, 11, 12, 13, 15, 20, 21, 23, 24 and 29. On the other hand the titer of both chorionic gonadotrophin and estrogens increased as the disease progressed or until death approached in cases 3, 7, 8, 9, 14, 17, 22, 25 and 28, except in cases 3, 14 and 25 in which only one determination of the total estrogens was done.

Discussion

The relationship between the estrogens and the cancer problem is well established at the present time. While the methods for the determination of these substances leaves something to be desired, nevertheless, we have used the method of Cohen and Bates[1] which has given good results in our hands.* We feel that the estimation of the total estrogens should also be carried out in the urine of patients suspected of having a malignancy since a number of workers have shown that even in urines from those having chorionepitheliomas the test for chorionic gonadotrophin may be negative.[2-8] Our results over a number of years suggest that this is due to an insufficient amount of the hormone being present in the 24 hour output of urine. For this reason we always concentrate the hormone in the urine by acetone precipitation.

Many cases of tumors of the endocrine system have been extensively reported in the medical literature. Strong, et al[9] showed that a transplantable ovarian tumor in mice produced appreciable amounts of estrogens. Butterworth[10] showed that tumors of the ovary in mice following irradiation showed estrogenic activity. Tumors of the testes in dogs were observed to "feminize" their host by Greulich and Burford[11] and by Burrows, et al[12] in man. Dingmanse, et al[13] noticed high levels of estrogen in the blood of men and women suffering from cancer while others showed normal amounts. The greatest concentration of the estrogens were found in prostatic and uterine tumors. Likewise Lewis and Geschickter[14] observed large amounts of estrogens in certain mammary and uterine tumors. Similar results were reported by Frank[15] in adrenal cortical carcinoma. Smith and Emerson[16] observed that five of seven postmenopausal women with mammary cancer excreted nearly five times the normal amounts of estrogens and they concluded that this was due to metastatic cancer. Similar reports were published by Pincus and Graubard[17] and by Dao,[18] Hodgson,[19] Meigs,[20] Taylor,[21] and Novak and Yui[22] showing that granulosa and theca cell tumors in postmenopausal women secreted estrogens.

Of further interest in this connection are the results of Fishman, et al[23-26] that different malignant tumors may contain up to 3600 per cent increase above normal of the enzyme beta-glucuronidase and that this was related to their high estrogen content, since the estrogens are to a large extent excreted as conjugated glucuronates in the urine. Further information may be obtained from the reviews of Huggins,[27] Griboff,[28] Gordan,[29] Burrows,[30] and Burrows and Horning.[31]

The question arises as to how it is possible to secure such a high degree of accuracy with the chorionic gonadotrophin and estrogen titers in the urine in the above cases. Zondek[32] showed in 1935 that genital tumors in women would show a positive Ascheim-Zondek pregnancy test in 86 per cent of the cases. In nongenital tumors in women this value

*We are now removing background material of the urine in these estrogen determinations.

was 36 per cent and in men it was 13 per cent. If none of these female patients were pregnant, it leaves only the malignant tumor itself as the source of the hormones the excess which is then excreted in the urine.

There are two important technical points in these tests for malignancy, (1) the urines are concentrated by acetone precipitation, and (2) the chorionic gonadotrophin is digested out by chymotrypsin leaving the anterior pituitary gonadotrophins, polysaccharides, etc., in the residual gonadotrophin fraction.

There is an inverse relationship between the excretion of the chorionic gonadotrophin and total estrogens in normal pregnancy, while in malignancy, in many cases, they increase together in the urine showing that the malignant tumor is producing both. This also indicates the presence of tissue capable of hormone production similar to cytotrophoblastic and syncytial trophoblastic tissue with the three exceptions shown in table 3. Thus the malignant tumor may be considered, from the physiologic point of view, to be a misplaced gland of internal secretion. Since the titer of chorionic gonadotrophin and estrogens generally increase as generalized metastases occur and death approaches, it is also possible that the amount of tumor tissue present in the patient, or the degree of malignancy of the tumor, may be directly proportional to the hormone titer in the urine.[33, 34]

In conclusion the data listed above would indicate that the results of the biochemical tests for chorionic gonadotrophin and estrogens (except for urines in pregnancy, postpartum conditions, hydatidiform moles, acromegaly, uncontrolled diabetes, and in diseases of the liver) would assist the clinician in the following ways:

1. In supplementing the clinical and pathologic diagnosis of malignancy,
2. In differentiating between the presence of a benign as against a malignant tumor,
3. In testing for the presence or absence of metastasis after treatment, and
4. In detecting presymptomatic cancer bearers before clinical evidence of the presence of the tumor is possible, a fact of much importance in any cancer control program.

Summary

Preliminary results in 51 cases of proven malignancy were used for diagnostic, and 29 cases for prognostic purposes. Excretion of chorionic gonadotrophin was increased above 30 mg. per 24 hr.* in 94 per cent of the cases while the excretion of the total estrogens was increased in 90 per cent. An increase in either one or both occurred in 100 per cent of the cases. Prognosis (not final) was good in eight cases after operation showing no chorionic gonadotrophin in the urine. The presence of a possible metastasis was indicated in 11 cases, while in 9 cases the titers or both chorionic gonadotrophin and total estrogens increased as the disease progressed until death. A brief discussion of the diagnostic and prognostic possibilities of the tests was given.

*Equivalent to 2.4 mg. chorionic gonadotrophin.

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Discussion (Abstract)

Dr. Charles L. Green, Dallas, Tex. There is a definite need at the present time for a quantitative biochemical test for chorionic gonadotropin to augment the biologic tests now employed. The assay must be simple enough to be carried out in the average clinical laboratory. The procedure described by Drs. Terrell and Beard appear to fulfill this need.

The preliminary studies presented concerning the excretion of chorionic gonadotropin in cases of malignancy are of great interest and this work should be expanded until enough cases are accumulated for statistical evaluation. It would appear from the data presented that the greatest benefit of the test may lie in the detection of viable tumor tissue after treatment, since in these cases variations from an established base line can be followed.

Since the quantity of urinary chorionic gonadotropin is increased in association with such a variety of malignant neoplasms i.e.,—carcinomas, melanomas, neuroblastomas and lymphomas, it remains to be proven that the authors are correct in assuming that the neoplasm produces this hormone; or if in some way neoplastic tissue alters the body's normal mechanism of production and excretion of this hormone.

UP TO THE PRESENT

Treatment of Hypertension: Part II.

Pharmacology and Therapy* (*Continued*)

JOHN H. MOYER, M.D., and EDWARD W. DENNIS, M.D., *Houston, Tex.*

WHETHER HYPERTENSION is secondary to renal disease or "idiopathic," one may assume that either an abnormal number or an abnormal type of vasoconstrictor impulse is implicated in the disease process. This assumption is based primarily on pharmacologic evidence.† The impulses pass from higher centers via the vasoregulatory areas (vasomotor center) and the sympathetic nervous system to the blood vessel to initiate vasoconstriction. The various drugs which reduce blood pressure apparently act by blocking the passage of vasoconstrictor impulses predominantly at a single point. This block is a partial one, and alterations in dosage produce proportionate alterations of effects. It can be assumed that judicious reduction of the blood pressure is of benefit in forestalling the progression and complications of hypertensive vascular disease, at least when the hypertension is severe.

As discussed in the initial installment of this series, there are three points in the autonomic nervous system at which the vasoconstrictor impulses responsible for hypertension may be blocked. According to this simplified type of presentation, they may be blocked, (1) centrally in the cortical area and vasomotor center, (2) at the ganglion, and (3) at the neuro-effector site (adrenergic blockade). The Rauwolfia preparations, hydralazine and the veratrum derivatives act centrally to suppress formation of vasoconstrictor impulses and to block the passage of these through the vasomotor center. Agents which produce ganglionic blockade (of both sympathetic and parasympathetic ganglia) are the quaternary ammonium compounds, hexamethonium, tetra-ethylammonium and pentolinium, and the newly introduced secondary amine, mecamylamine (Inversine). Drugs which produce a block of vasoconstrictor impulses at the neuro-effector site (adrenergic blockade) include Benzodioxane, phenoxybenzamine (Dibenzyline), phentolamine (Regitine), Dibenamine and a dihydrogenated ergot preparation (Hydergine).

General Pharmacodynamic Considerations

To illustrate the scope of antihypertensive drug therapy, each of the three groups (central, ganglionic and peripheral) of compounds under consideration, will be presented in a general fashion. Following this, each major drug will be presented in terms of its best use in treating hypertension. Some drugs are effective when used alone. Other such as hexamethonium, hydralazine (Apresoline), and pentolinium (Ansolysen) are difficult to control when used alone, and are most advantageous when used in combination with other agents.

Central Agents. The central agents, veratrum, hydralazine and Rauwolfia, block or suppress vasoconstrictor impulses in the central nervous system at the hypothalamus and/or vasoregulatory (vasomotor) centers (Fig. 6). They do not markedly block the reflexes which occur with changes in posture so that the blood pressure reduction achieved by them is present in all positions, not just the erect position. In general, they exert only a mild to moderate effect on the blood pressure when given orally. Excessive hypotension after either the oral or parenteral route may be rapidly combatted with norepinephrine or any other effective vasopressor agent. Each of these hypotensive agents has unpleasant

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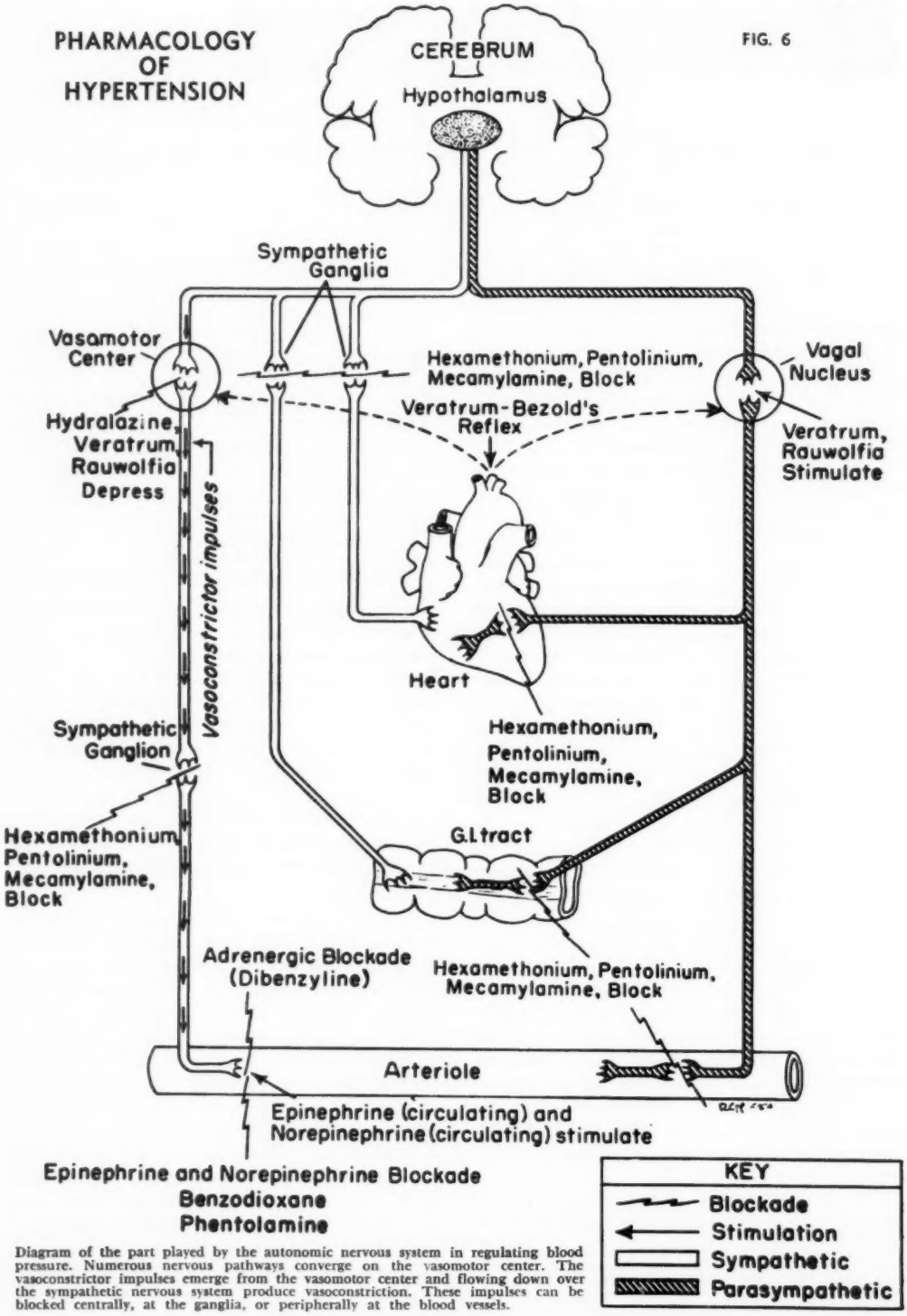
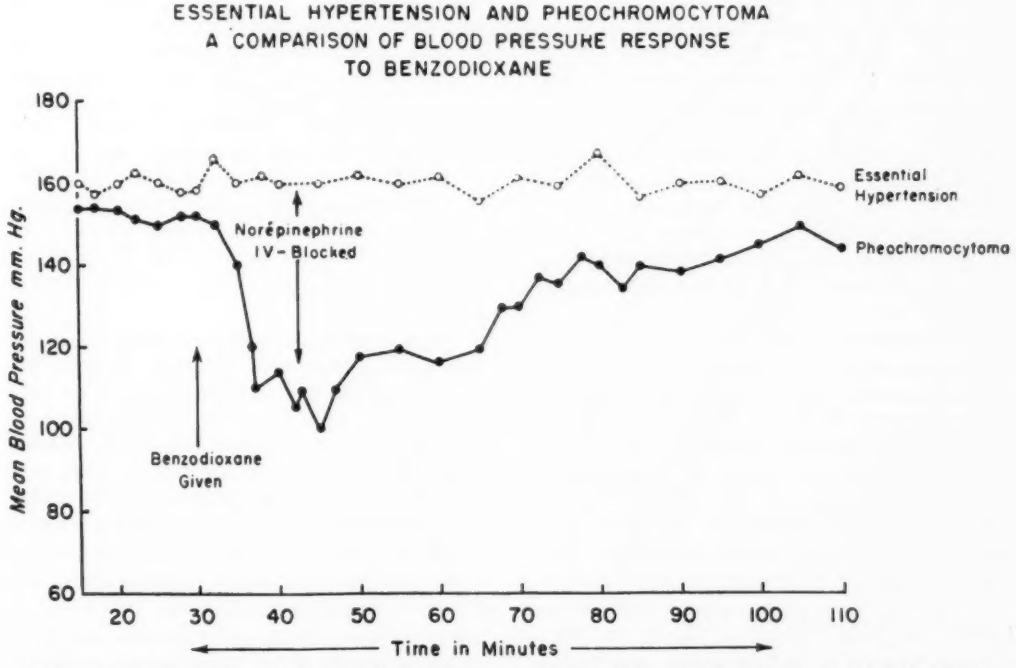


Diagram of the part played by the autonomic nervous system in regulating blood pressure. Numerous nervous pathways converge on the vasomotor center. The vasoconstrictor impulses emerge from the vasomotor center and flowing down over the sympathetic nervous system produce vasoconstriction. These impulses can be blocked centrally, at the ganglia, or peripherally at the blood vessels.

side effects which will be described in greater detail later. Veratrum derivatives stimulate the emetic center so that vomiting commonly occurs when a therapeutic dose is reached. More purified preparations have been introduced recently to obviate this, but vomiting continues to be a common problem with veratrum therapy. Chlorpromazine (Thorazine) has been used with veratrum without significantly lessening the incidence of vomiting.[19] Hydrazaline stimulates the cardioaccelerator nerves producing tachycardia when used alone.[8] Palpitation is a frequent complaint, and patients with coronary artery disease have been reported to have a higher incidence of anginal episodes and even myocardial infarction.[8] This effect on the cardioaccelerator nerves is blocked with Rauwolfia or any of the ganglionic blocking agents. This suggests that hydralazine should never be used alone.[20] Headaches are a common accompaniment of hydralazine therapy, and with large dosage a febrile illness akin to collagen disease has been reported.[21] The untoward effects of Rauwolfia are not of such serious import but are none the less annoying. Common ones include nasal congestion, somnolence, Parkinsonism, and rarely, a severe psychogeni-agitated depression reaction.[22]

Ganglionic Agents. The quaternary ammonium compounds hexamethonium, tetraethylammonium and pentolinium are absorbed rather poorly from the gastrointestinal tract so that regulation of oral therapy is difficult. Mecamylamine on the other hand is readily and completely absorbed from the gastrointestinal tract rendering it much more effective. All ganglionic blocking agents interfere with reflexes responsible for adjusting the blood pressure to postural change. Therefore, these agents reduce the erect blood pressure more than the supine blood pressure. All produce a parasympathetic as well as sympathetic blockade (Figs. 6 and 8). Therefore, constipation, urinary difficulties, and dryness of the mouth are common complaints in addition to postural dizziness and syncope. Excessive hypotension may be combatted with

FIG. 7



Comparison of two patients with elevated blood pressure, one with essential hypertension and the other with a pheochromocytoma. When Benzodioxane was given to each, there was no effect on the patient with essential hypertension but there was a sharp reduction in blood pressure in the patient with pheochromocytoma due to blockade of the circulatory vasopressor material. Norepinephrine, when injected intravenously into each patient immediately after the administration of Benzodioxane did not produce a rise in blood pressure.

norepinephrine or any other pressor agent (Fig. 6).

Adrenergic Blocking Agents. Adrenergic blocking agents block the transmission of impulses from the postganglionic ending to the effector site (Fig. 6). One recalls that sympathin (norepinephrine and epinephrine) is liberated at the neuro-effector site, and also that epinephrine and norepinephrine are disseminated humorally throughout the body. The adrenergic blocking agents in low concentration produce a humoral blockade of circulating epinephrine and norepinephrine (Fig. 7). Because of this fact, they are useful in low dosage as a diagnostic test for pheochromocytomata. In larger dosage, they produce a true adrenergic blockade at the neuro-effector site in addition to the humoral blockade. With adrenergic blockade, as with ganglionic blockade, the blood pressure reduction is primarily postural. In addition to this, these compounds block norepinephrine or any other pressor agent given to combat excessive hypotension. The only effective antidote to their use is to lower the head of the bed until the effects of the drug wear off. With the exception of Dibenzyline, the adrenergic blocking agents which include Regitine, Hydergine, Benzodioxane and Dibenamine, are not dependable when given by mouth. An additional difficulty is that tolerance to the drugs develops quickly. Therefore, they are not effective when used for the treatment of clinical hypertension. Dibenzyline has been used both alone and in combination with Rauwolfia, the latter being a most useful and potent hypotensive combination. The chief use of Benzodioxane and Regitine is as a diagnostic test for pheochromocytomata (Fig. 7).

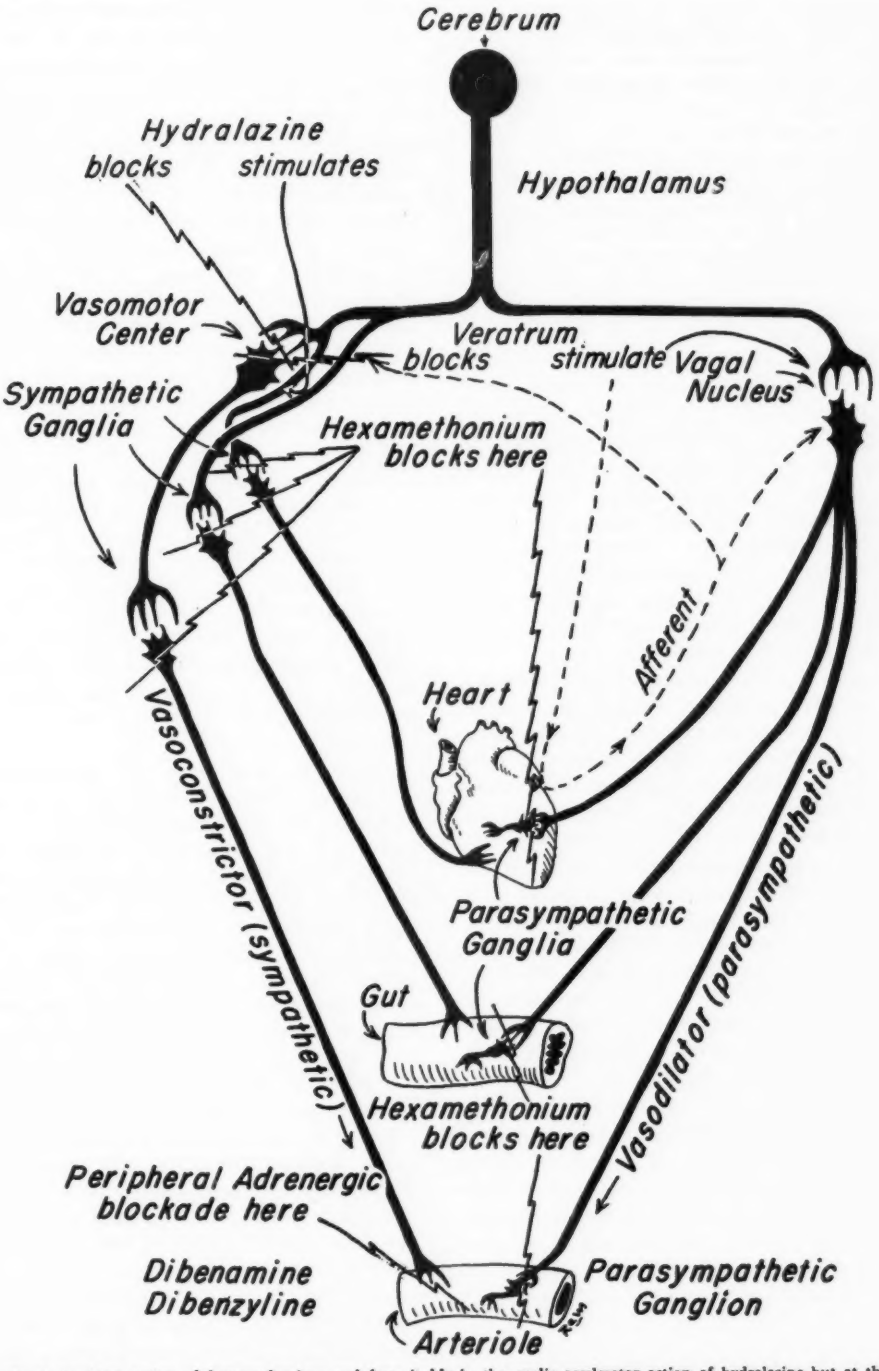
Combination Drug Therapy. The overall picture of autonomic blocking agents suggests that virtually all have some undesirable effects as well as some advantages. In general, the more potent the agent, the more difficult it is to administer. It has been postulated, therefore, that by giving two or more agents concomitantly, one might achieve an additive hypotensive effect and, at the same time, a reduction of the undesirable side effects which are noted when any one of the drugs is used alone. There are several notable examples of this, either hexamethonium, pentolinium or Rauwolfia will block the cardioaccelerator effect of hydralazine[20] (Fig. 8). Rauwolfia, when used in combination with ganglionic or adrenergic blocking agents will permit a lower dosage of the more potent agents to be used and thus reduce some of the untoward effects of ganglionic or adrenergic blocking agents.[23] At this writing, experience suggests that Rauwolfia should form the background or base medication for the initiation of treatment of all degrees of hypertension to which other agents are added as necessary. Patients with mild or labile hypertension will sometimes become normotensive on Rauwolfia alone. If the response is suboptimal, a more potent antihypertensive agent may be added to Rauwolfia. With severe or rapidly progressive hypertension, Rauwolfia plus a more potent agent should be started together from the outset of therapy. Preliminary studies suggest that perhaps mecamylamine may be an exception to this general rule.

Central Agents

Veratrum viride. The liliaceous plant, veratrum viride, contains a number of alkaloids of varying hypotensive potency. The pharmacology of crude extracts of veratrum as well as the alkaloid protoveratrine, was studied before the turn of the century. Eden described the effects of protoveratrine in 1892, and Pesci in 1906 reported that veratrum lowered blood pressure within 7 to 50 minutes after administration. The tendency to produce vomiting at the therapeutic level has limited its usefulness, although in the past few years, purification of these extracts has led to an increase in their clinical use.

PHARMACODYNAMICS. Veratrum preparations have: (1) a direct central action on the vasomotor center which diminishes centrally mediated vasoconstrictor impulses; (2) a reflex action through stimulation of afferent vagal nerve endings arising in the left ventricle and, to a lesser extent, in the lungs and carotid sinus (Fig. 6). Impulses are transmitted to the vagal nucleus and vasomotor center via the vagus nerve (afferent limb) and return via vagal fibers (efferent limb) to cause bradycardia and, via an unknown pathway, to cause reduction in blood pressure. Observations on hemodynamics indicate an unchanged to increased cardiac output.[24] The

FIG. 8



Ganglionic blocking action of hexamethonium and how it blocks the cardio-accelerator action of hydralazine but at the same time reinforces the hypotensive action of the hydralazine. Thus the blood pressure is reduced with a minimal increase in pulse rate.

TABLE 1[27]

A COMPARISON OF TWO VERATRUM EXTRACTS CONTAINING MULTIPLE ALKALOIDS WITH THE PURE ALKALOID PROTOVERATRINE

Preparation	*Number of Patients Treated*	*Response Rate Per Cent*	*Normotensive Rate Per Cent*
Alkavervir (Veriloid)	30	50	7
Vergitryl	31	19	3
Protoveratrine	23	17	13

reduction in blood pressure, then, is due to a decrease in peripheral resistance. Splanchnic and renal blood flow are not affected after an initial fall. The fact that cerebral blood flow is maintained despite the reduction in arterial blood pressure[25] indicates a reduction in cerebrovascular resistance (mean blood pressure divided by cerebral blood flow).

SIDE EFFECTS. All currently available veratrum preparations have a prominent emetic effect which is central in origin. The margin between hypotensive and emetic dosage is narrow. Concomitant administration of chlorpromazine (Thorazine) in this clinic did not appreciably reduce this emetic effect. A similar experience has recently been reported from the Cleveland Clinic.[26]

CLINICAL USE IN THE OUTPATIENT MANAGEMENT OF HYPERTENSION. Several semipurified extracts of veratrum and two purified alkaloids, protoveratrine and cryptenamine have been used rather extensively during recent years. Results with veratrum extracts have not been very good in our clinic (Table 1).

Wilkins administered alkavervir to 20 patients for 6 to 20 weeks and achieved a 70 per cent response rate.[28] He noted that on continued administration there was no evidence of tolerance or idiosyncracy to the drug. When used orally, the initial dose of alkavervir is 1 mg. given 4 times daily, protoveratrine, 0.2 mg. given 4 times daily, and cryptenamine 2 mg. given 4 times daily.

Because of the high incidence of toxicity, a variety of agents including chlorpromazine, Dramamine and tincture of belladonna, and methamtheline (Banthine) have been administered concomitantly with a varying degree of success.[29] Protoveratrine has been combined with phenoxybenzamine and Rauwolfia* in the oral treatment of hypertension.[30]

*Available as 'Mio-Pressin' by Smith, Kline & French Labs., Philadelphia, Pa.

In our opinion, the currently available oral veratrum preparations have little place in the therapy of hypertension.

PARENTERAL THERAPY. Intravenous alkavervir and protoveratrine are exceedingly potent and useful preparations in the short-term management of hypertensive emergencies. A significant reduction of blood pressure can be obtained in virtually all patients who can tolerate the agent.[31] In treating hypertensive crisis, a useful method for giving alkavervir is as follows. An initial priming dose consisting of 0.5 gamma per kg. of body weight per minute is given intravenously until a satisfactory reduction in blood pressure is obtained, or for a maximum of 20 minutes if no reduction occurs. Then 4.0 mg. of alkavervir in a liter of 5 per cent glucose in water is infused at the rate of 10 to 100 drops per minute, depending upon the blood pressure response. An infusion of norepinephrine containing 4 mg. per liter should be prepared beforehand and connected through a Y-tube for immediate infusion should the blood pressure decrease excessively at any time (Fig. 9). Some EKG abnormalities at the upper dosage range, which were related to the vagal effect of veratrum and which could be blocked with atropine, have been reported.[32]

Alkavervir may be given intramuscularly with great efficacy, particularly in situations in which the immediate reduction in blood pressure is not mandatory. An initial dose is 0.6 mg. intramuscularly. The blood pressure should be recorded every 15 minutes thereafter. If there is no response to this dose, subsequent injections may be given at 2 to 3 hour intervals with increments of 0.1 mg. to 0.2 mg. per injection until the desired response is obtained. Atropine will combat excessive bradycardia should it develop. After a response is obtained, the interval between dosages depends upon the duration of effect.

SUMMARY OF VERATUM THERAPY. The following points are important with regard to veratrum preparations. (1) Veratrum preparations, whether alkaloids or semipurified extracts, are of limited value when given orally in treating hypertension because of the narrow range between therapeutic effect and emetic effect. (2) Alkavervir or pure veratrum alkaloids such as protoveratrine, may be used effectively when given parenterally for the

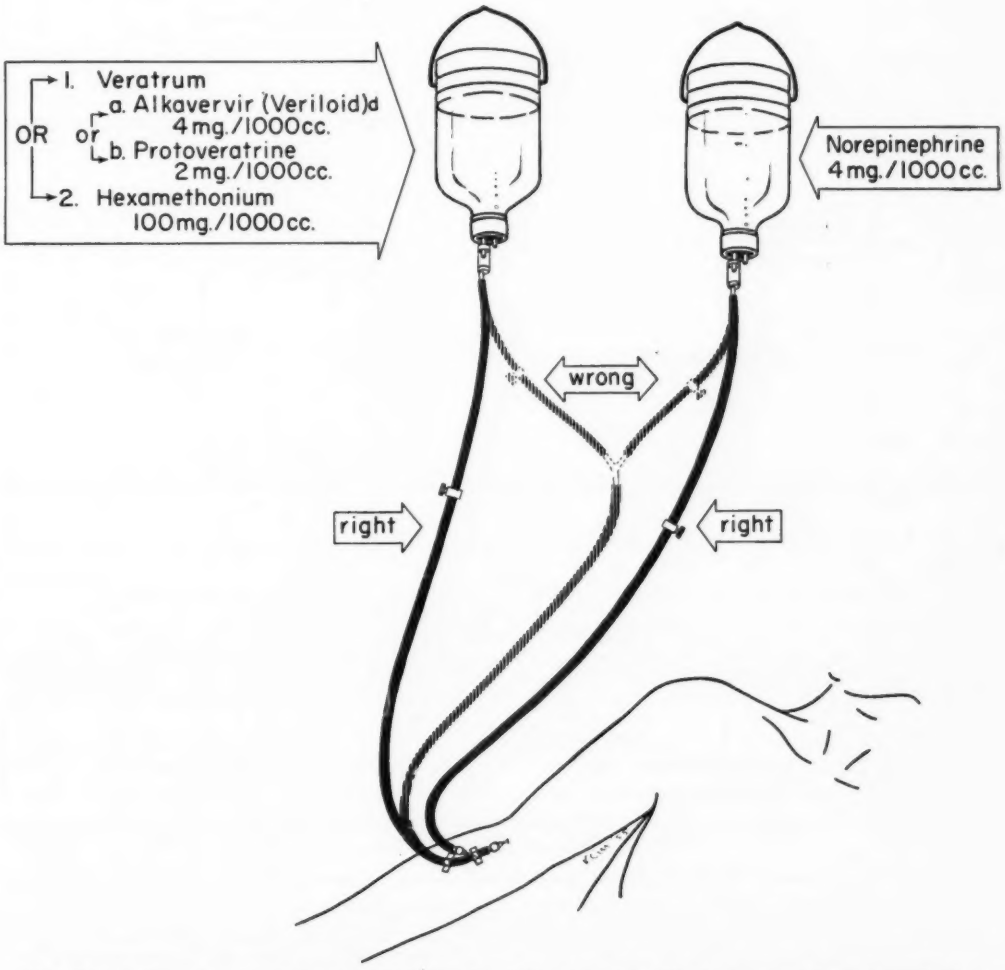
treatment of hypertensive crisis and may be given by continuous infusion over a four to five day period or intramuscularly.

Hydralazine (Apresoline). This is a centrally acting agent which may be given both orally and parenterally. Its hypotensive properties were discovered in the course of testing it as an antimalarial drug.[33]

PHARMACODYNAMICS. The pharmacology of hydralazine is not completely understood, but the best evidence suggests a central site of action in the mid brain and/or medulla (Figs. 6 and 8). This results in a true vasodepressor response in experimental animals and in normotensive and hypertensive human subjects. It also has a centrally mediated sympathomimetic effect on the heart as indicated by an increase in pulse rate and cardiac output[34] (Figs. 10A and 10B). This has been responsible for some of the more serious side

FIG. 9

APPARATUS FOR CONTINUOUS INFUSION OF VERATRUM OR HEXAMETHONIUM

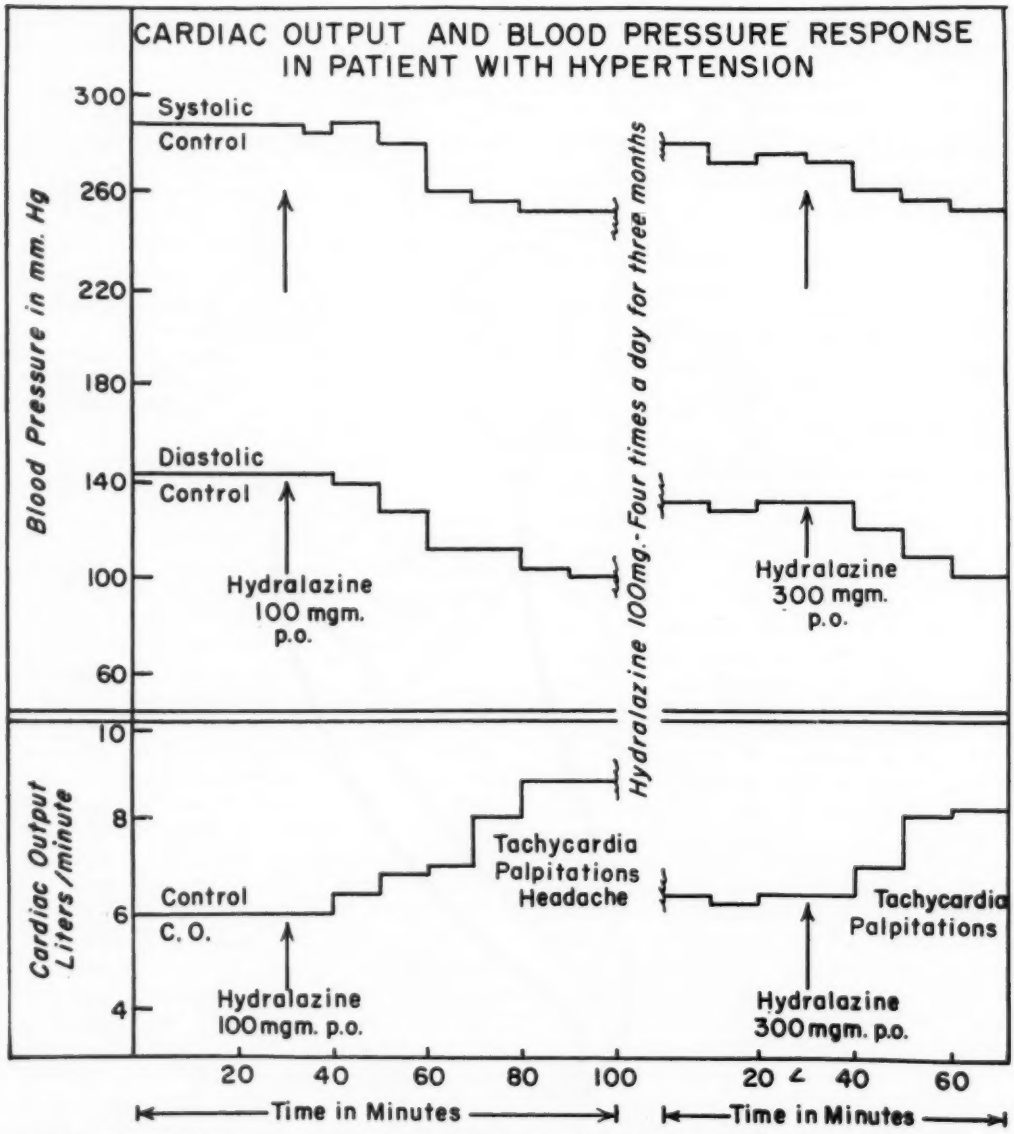


Method for setting up continuous intravenous infusion of veriloid or ganglionic blocking agents such as hexamethonium.

reactions of the drug such as palpitation, angina and occasionally myocardial infarction. This cardio-accelerator effect can be blocked with Rauwolfia, surgical sympathectomy,[35] and ganglionic blocking agents.[34] When Rauwolfia or ganglionic blockade is to be used in combination with hydralazine, this should be started prior to the hydralazine in order to prevent the tachycardia.

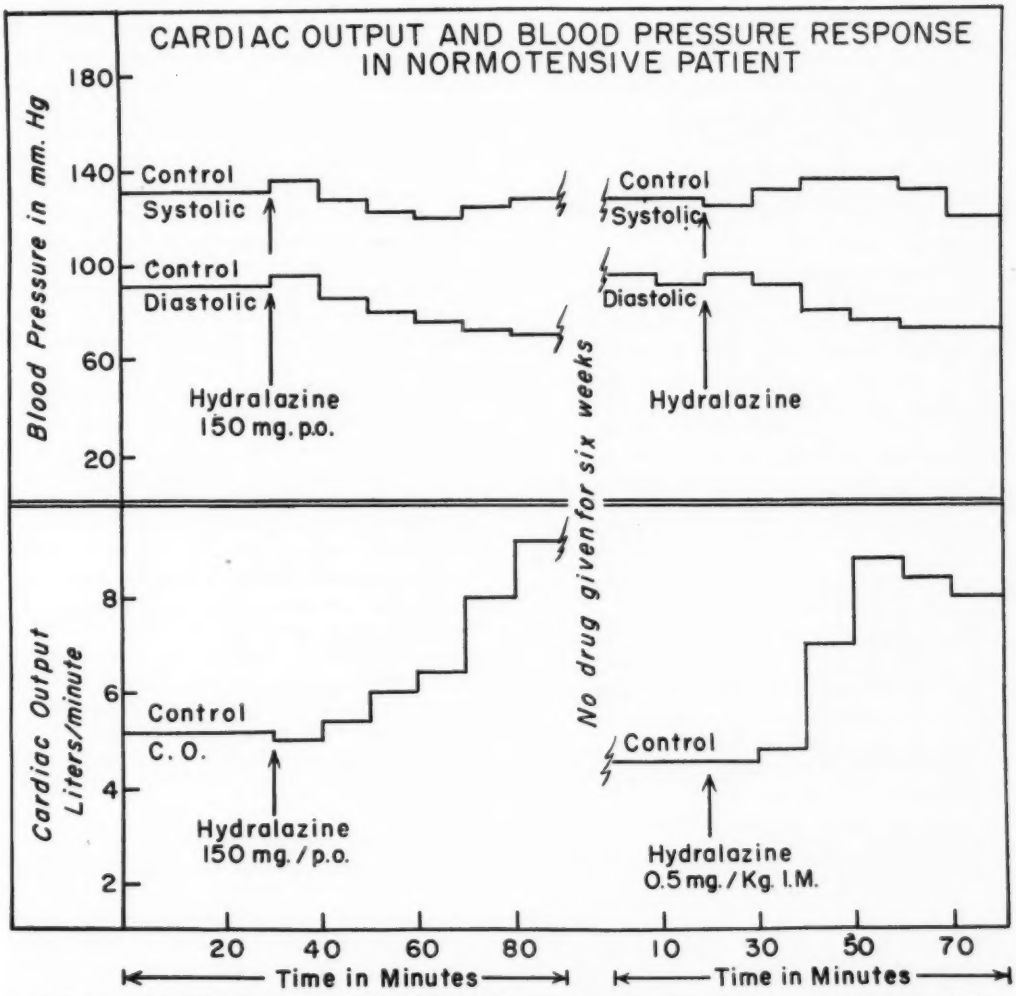
One of the more desirable effects of hydrala-

FIG. 10, A



Cardiac output and blood pressure response to oral administration of hydralazine in a patient with essential hypertension. There is an increase in cardiac output associated with blood pressure reduction, headache, palpation, and tachycardia. After the patient had taken this same dose four times a day for three months, the tachycardia, palpation, and headache were absent and the cardiac output had returned to the control levels. However, the blood pressure was also increasing toward the control levels. When the dose of the drug was increased (to 300 mg.) a response similar to the initial one (100 mg.) was obtained. (Courtesy A.M.A. Arch. Int. Med. 91:16, 1953.)

FIG. 10, B



Cardiac output and blood pressure response to hydralazine in a patient with normal blood pressure. Following an initial test dose of 150 mg. given orally, there was a sharp increase in cardiac output associated with a reduction in blood pressure. The diastolic pressure response was more prominent than the systolic. Six weeks later a test dose of the drug was given parenterally with a similar response of the diastolic pressure but there was a more abrupt increase in cardiac output associated with a slight initial rise in systolic pressure followed by a fall. The onset of action was less delayed than after oral administration. (Courtesy of A.M.A. Arch. Int. Med. 91:14, 1953.)

zine is its ability to increase renal plasma flow while producing no significant alterations in glomerular filtration rate.[36] Hydralazine reduces cerebrovascular resistance without reducing cerebral blood flow unless excessive hypotension is produced.[37]

Side Effects. The most common untoward effects of hydrazaline are palpitation, angina, and even frank myocardial infarction, attributable to its stimulation of the cardioaccelerator fibers. The latter may be blocked with Rauwolfia or ganglionic blocking agents.[38] Headaches, apparently caused by hydralazine, occur occasionally. The mechanism for their production is poorly understood.

A rheumatic and febrile syndrome which, in its more severe form, simulates lupus erythematosus occurring during prolonged hydralazine therapy has been reported[21] and is related to magnitude and duration of dosage. Characteristically, it has subsided on

withdrawal of drug which may be restarted later in lower dosage.

CLINICAL USE. The blood pressure response consists of a greater fall in diastolic than systolic pressure, with a slight orthostatic component. Orally, the dosage is 25 mg. four times daily with meals and at bedtime, increased until a satisfactory blood pressure response is obtained. One thousand milligrams per day is the maximum dose that should be employed.

Tolerance appears to develop to oral therapy unless it is interrupted. In our series, 35 per cent of 54 patients were responsive to hydralazine alone after three months.[8] After one to two years of therapy, the number responding was reduced to 9 per cent. In another series of patients, 57 per cent of 33 patients had a satisfactory reduction in blood pressure after one year or more of hydralazine therapy, although if patients with grade IV hypertension were included, this figure drops to 50 per cent.[40] In this series, only 25 per cent of those who originally started on hydralazine continued to take it for a year. These figures hint at the difficulties of keeping patients on this form of therapy.

Rauwolfia may be added to hydralazine (the Rauwolfia should be started first as indicated in order to block the cardioaccelerator effects of hydralazine), yielding a combination which will effect a greater reduction in blood pressure than would be obtained with either alone. The hydralazine should be started in small doses, i.e., 25 mg. four times daily, and increased by a titration method until an optimal reduction in blood pressure is obtained. The dosage of hydralazine should be regulated by the blood pressure readings in the upright position. In a small group of patients thus treated by the authors, 67 per cent responded to treatment and 18 per cent became normotensive.[23]

The dose of hydralazine, used alone or in combination with Rauwolfia, averages 300-350 mg. per day, with a range up to 1 gram per day. If no response is obtained in two to three months, or if untoward effects preclude adequate dosage for blood pressure reduction, hydralazine therapy should be abandoned.

Hydralazine, although of limited value when administered by the parenteral route, is useful in the treatment of acute glomerular nephritis and toxemia of pregnancy[39] in which diseases it enjoys some specificity of action. Best results are obtained when this drug is used in combination with reserpine. The onset of action (15 to 20 minutes) of hydralazine after parenteral administration is much more rapid than that of reserpine. Therefore, it is given to patients in whom a rapid onset of action is a necessity or in those who do not respond adequately to reserpine alone.

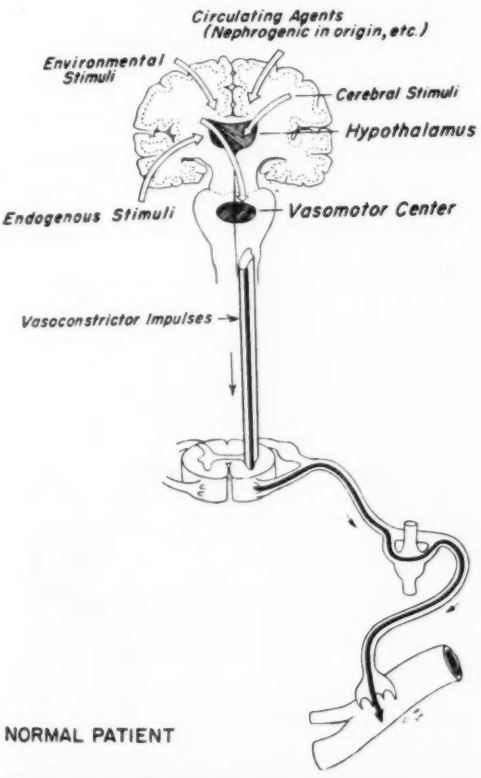
In toxemia of pregnancy, 5 to 10 mg. of reserpine are given concurrently or preceding the hydralazine. For optimum effect reserpine injections should be spaced from six to eight hours apart. This should be governed, of course, by the blood pressure response. If the response is inadequate, hydralazine is added to the regimen as a single intravenous or intramuscular injection of 10 to 20 mg. followed by a continuous intravenous infusion of 20 to 50 mg. diluted in 1000 cc. of 5 per cent dextrose in water. The continuous infusion is particularly desirable when the blood pressure is quite labile, as during labor. Although most patients will respond to reserpine alone, hydralazine should be added when a more rapid effect is desired and when a more marked fall in blood pressure is needed. Even though hydralazine alone is effective in these patients, reserpine counteracts the tachycardia of hydralazine and aids in maintaining the normotensive state as well as providing sedation.

Rauwolfia. In the latter part of the sixteenth century, Leonard Rauwolf, a German physician and botanist, studied medicinal plants in Asia and Africa which had been mentioned by early Greek and Arab physicians. The results of his investigation were published in 1582. Several years later when a new genus was added to the plant family Apcoynaceae, it was called Rauwolfia in his honor.[41, 43] At the present time, some 40 to 50 species of Rauwolfia have been described which grow in tropical and semitropical areas all over the world. Since the Indian chemists Siddiqin and Siddiqui[45] isolated the first crystalline alkaloid in 1931, about 14 alkaloids have been reported from *Rauwolfia serpentina* alone. The Rauwolfia compounds have been known to Indian medicine for centuries in the treatment of fever, insanity, neuroses and a variety of other disorders. The pharmacologic properties of an alkaloid isolated from

Rauwolfia serpentina were reported by Chopra, Gupta and Mukherjie in 1933. Chopra and Chakravarti in 1941[44] noted that crude extracts of *Rauwolfia serpentina* produced a fall in arterial pressure in both decerebrate and spinal preparations. Many studies during the past 20 years have given impetus to the use of Rauwolfia in the treatment of clinical hypertension.[42]

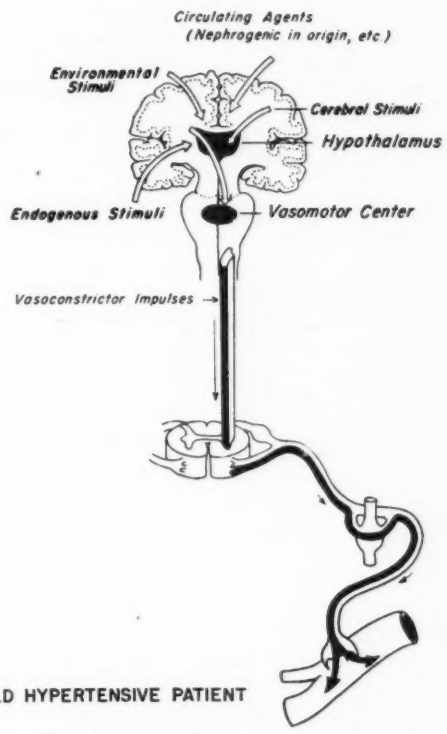
PHARMACODYNAMICS (GENERAL). The precise way in which *Rauwolfia serpentina* derivatives act is not known. Clinical and laboratory results suggest a central action at the vasomotor center and above. Plummer[45] in discussing the pharmacodynamics of the Rauwolfia alkaloid, reserpine, has considered that all observed effects of reserpine, including sedation, reduced emotional response, peripheral autonomic alterations, and circulatory changes are explicable on the basis of an alteration of the sympathetic, parasympathetic balance by partial suppression of sympathetic predominance at the hypothalamic level.[45]

FIG. 11, A



Diagramatic representation of vasoconstrictor impulse originating in the brain and traveling to the blood vessels in a normal subject. (Courtesy A.M.A. Arch. Int. Med. 96:540, 1955.)

FIG. 11, B

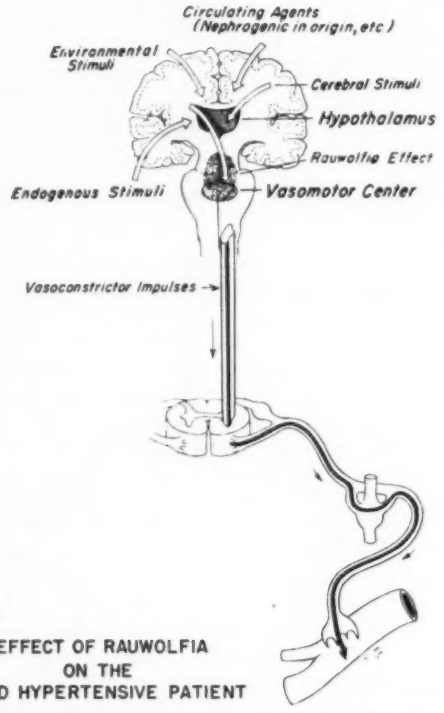


Mild hypertensive showing a mild to moderate increase in vasoconstrictor impulses traveling over the sympathetic nervous system to the blood vessels. (Courtesy A.M.A. Arch. Int. Med. 96:540, 1955.)

At the present, a rather large number of Rauwolfia preparations are available to the practitioner or under clinical investigation. Pure alkaloids of *Rauwolfia serpentina* which have been used to treat hypertension include reserpine, rescinnamine and recanescine. There are many extracts of the whole root of *Rauwolfia serpentina* containing multiple alkaloids, which vary primarily with regard to purity of extraction. In general, it can be said that all have a comparable effect upon the blood pressure and that all are pharmacodynamically similar. Variation appears to consist primarily in milligram for milligram variation in potency.[46]

SEDATION. All *Rauwolfia serpentina* preparations have a prominent sedative action, but somnolence is not so prominent as with barbiturates. Frequently, a tolerance appears

FIG. 11, C



EFFECT OF RAUWOLFIA
ON THE
MILD HYPERTENSIVE PATIENT

Rauwolfia depresses vasoconstrictor impulses centrally in the mild hypertensive resulting in a normal outflow of these impulses over the sympathetic nervous system to the blood vessels. The blood pressure returns to normotensive levels. (Courtesy A.M.A. Arch. Int. Med. 96:540, 1955.)

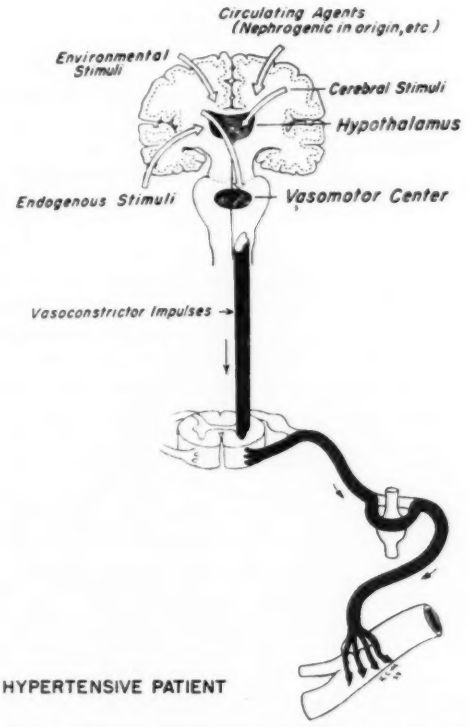
to develop to sedation, and this bears no relation to the blood pressure response. Sedation may appear without a reduction in blood pressure in some, while others experience a sharp reduction in blood pressure without sedation. Frequently, when the two coexist, sedation will disappear with no change in the blood pressure response. In contradistinction to this, one occasionally encounters severe mental depression with reserpine therapy.[22]

CARDIOVASCULAR EFFECTS. Bradycardia is a commonly observed effect which cannot be blocked with atropine and is therefore not entirely vagal. Experimentally, there is little alteration in the cardiac output in dogs after intravenous reserpine. The blood pressure is reduced primarily as a result of peripheral vasodilatation, due to a reduction of vasoconstrictor impulses from the vasomotor center.[45] The drug is equally effective in mild and severe hypertension, although when normotensive levels are restored by treatment, it is usually in patients with less severe disease.

RENAL EFFECTS. Renal hemodynamics and electrolyte excretion were studied after intravenous reserpine to dogs and after oral and intramuscular administration to hypertensive patients.[47] There was no significant alteration in renal blood flow, glomerular filtration rate or renal excretion of water and electrolytes except for a slight depression of the glomerular filtration rate at the point of maximal blood pressure reduction after intravenous administration to patients with hypertension (Figs. 11A, B, C, D, and E).

SIDE EFFECTS. The side effects of some pure alkaloids and extracts containing multiple alkaloids, are compared in table 2. Bradycardia, increased appetite, nasal congestion, and some measure of sedation to drowsiness were common effects. The extreme mental depression mentioned earlier is an uncom-

FIG. 11, D



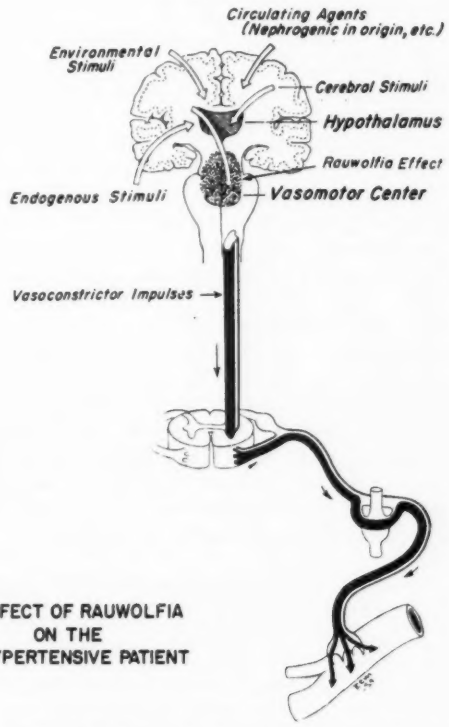
HYPERTENSIVE PATIENT

In the patient with severe hypertension there is a marked increase in outflow of vasoconstrictor impulses over the sympathetic nervous system to the blood vessels. This produces vasoconstriction with a marked rise in blood pressure. (Courtesy A.M.A. Arch. Int. Med. 96:541, 1955.)

mon but serious complication, thus far reported primarily with reserpine administration. Reports differ as to the benefits associated with concomitant administration of an antihistaminic to reduce nasal congestion. Kohlstaedt has reported less nasal congestion when an antihistaminic was given regularly with Rauwolfia. Others have felt that little benefit was derived from this.

CLINICAL USE. *Rauwolfia serpentina* preparations thus far studied are only moderately effective in their ability to reduce blood pressure after prolonged oral administration. A wide range of dosage is mentioned in the literature with little variation in the rate of response. An accepted dosage is 1.0 mg. reserpine per day given in 2 to 4 divided dosages. The approximate equivalents to this reserpine dosage are listed in tabular form. Quantitation of most Rauwolfia preparations is by a bioassay technic which is difficult.

FIG. 11, E



EFFECT OF RAUWOLFIA ON THE HYPERTENSIVE PATIENT

When Rauwolfia is given to the patient with severe hypertension, there is a significant reduction in blood pressure due to central depression of the sympathetic nervous system. However, this effect is usually not great enough to reduce the blood pressure to normotensive levels. As a result the patients remain moderately hypertensive. (Courtesy A.M.A. Arch. Int. Med. 96:540, 1955.)

In the opinion of the authors, a *Rauwolfia serpentina* preparation should form the background of therapy for all patients with medically managed hypertension. In this fashion, persons who obtain an adequate blood pressure response to Rauwolfia alone are not subjected to more intensive therapy. In those who do not respond optimally, Rauwolfia may be used in combination with a more potent agent. Some of the undesirable effects of therapy with other hypotensive agents may be blocked with Rauwolfia, and the Rauwolfia also has a potentiating effect, permitting a smaller (and therefore less troublesome) dose of the adjunctive agent. The blood pressure response following both pure alkaloidal preparations and extracts of the whole root of *Rauwolfia serpentina* is slow in onset and the maximum effect is not seen for one to seven days with reserpine and two to three weeks with the alseroxylon fraction of the whole root. Following parenteral administration of reserpine and rescinnamine, however, the onset of effects is within several hours. This lag between administration and effect remains unexplained.

The alkaloids, reserpine and rescinnamine, may be given either intravenously or intramuscularly. Doses of 2 to 10 mg. will effect a moderate to marked reduction in the supine blood pressure in one to three hours which will persist for 4 to 12 hours.

CLINICAL RESULTS (ORAL THERAPY). Following therapy with oral Rauwolfia alone, approximately 40 to 50 per cent will have a significant reduction in average mean blood pressure. About 10 to 15 per cent will become normotensive on Rauwolfia alone, and almost all of these will come from the group with mild blood pressure elevation.

The dosage of Rauwolfia preparations depends primarily upon the degree of purity of the extract. Three of the pure alkaloids thus far investigated clinically seem comparable on a milligram for milligram basis. Using one milligram of reserpine as a reference value, a convenient and reasonably accurate table of equivalents would be as follows:

Reserpine 1 mg. =	Alseroxylon (Rauwiloid)	4 mg.
	Roxinil	10 mg.
	Recanescine	1-1.5 mg.
	Rescinnamine	1-1.5 mg.
	Rauwolfia (Raudixin)	250 mg.

TABLE 2

SUMMARY OF PHARMACODYNAMIC RESPONSES (BENEFICIAL AND UNTOWARD) TO DIFFERENT EXTRACTS OF RAUWOLFIA USED IN THE TREATMENT OF HYPERTENSION

	Roxinil		*Alseroxylon*		*Rauwolfia (Whole Root)*		*Reserpine*		*Rescinnamine*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Total number patients treated	40	100	118	100	42	100	62	100	84	100
Response										
Beneficial*										
Blood pressure reduction		65		51		55		53		48
Bradycrotic response		70		65		74		77		55
Sedation		50		53		57		47		35
Sense of well being		40		57		50		35		27
Untoward*										
Nasal congestion		53		72		74		65		51
Diarrhea		13		6		7		5		7
Increased appetite		60		61		62		60		33
Weight gain		48		62		52		50		40
Fatigue and weakness		40		11		24		44		15
Dizziness		30		7		10		21		5
Nightmares		10		6		7		6		4
Dysuria		3		2		2		2		
Impotence		5		1		2		3		
Syncope								2		1
Muscular aches		8		1		5		10		

*Patients presenting side effect expressed as per cent of total number of patients treated with this particular drug.

In the management of clinical hypertension, as long as 1 mg. of reserpine or its equivalent is given per day a nearly maximal effect of oral Rauwolfia may be anticipated. A strikingly higher dose has not increased the response rate significantly, although a lesser dose may lower it. The onset of effect may vary from one to four weeks after the initiation of therapy. Rauwolfia, when given by mouth, does not produce an excessive reduction in blood pressure and will produce no lowering in a normotensive individual. Plummer recently reported a 20 month old child who ingested 200 mg. of crystalline reserpine at one time.[45] Although blood pressures were not quoted, there was apparently no clinical hypotension. There was some lethargy and somnolence for two to three days. The authors have observed a young girl who ingested about 150 to 200 mg. of alseroxylon with no subsequent reduction in blood pressure to hypotensive levels.

CLINICAL RESULTS (PARENTERAL THERAPY) The use of Rauwolfia parenterally has been limited to the pure alkaloids. Reserpine has been investigated more thoroughly than other alkaloids. Hafkenschiel and Sellars[48] found that 18 of 20 patients with hypotension showed a significant (20 mm. Hg. or greater) fall in mean arterial blood pressure. In eight of this group, the infusion was completed before the blood pressure response was obtained. The average latent period before onset of hypotensive effect was three and three-fourth hours. The authors have noted a 76 per cent response to intravenous reserpine with 53 per cent being rendered normotensive. In this study, the dosage was 1 to 2 mg. The most marked reduction occurred at about three hours after infusion corresponding to the above series.[49] Subsequently, average dosages of 5 to 10 mg. have increased the incidence of response to approach 95 to 100 per cent. Infrequently it is necessary to give up to 20 mg. intramuscularly or intravenously. There appears to be little difference in the rate of response whether given intramuscularly or intravenously. In contrast to oral reserpine, the magnitude of response to in-

TABLE 3

METHOD OF DOSE TITRATION OF MECAMYLAMINE

	Dose of Mecamylamine			
	7 A.M.	*12 Noon*	*5 P.M.*	*10 P.M.*
1st week	2.5 mg.		2.5 gm.	
2nd week	5 mg.		5 mg.	
3rd week	5 mg.	5 mg.	5 mg.	5 mg.
4th week	5 mg.	10 mg.	5 mg.	5 mg.
5th week	5 mg.	10 mg.	10 mg.	5 mg.
6th week	5 mg.	15 mg.	10 mg.	5 mg.
7th week	10 mg.	15 mg.	10 mg.	5 mg.

travenous reserpine appears directly related to the magnitude of the dose.

SUMMARY OF RAUWOLFIA. Currently, it appears that a Rauwolfia preparation should be employed in the treatment program of virtually all patients who are receiving autonomic drugs for the management of hypertension. Patients with mild or labile hypertension may become normotensive on Rauwolfia alone. If the response to Rauwolfia is suboptimal a more potent hypotensive agent may be added to the regimen. With severe or rapidly progressive hypertension, Rauwolfia and a more potent agent may be used in combination from the outset of therapy. As has been mentioned, Rauwolfia potentiates the effect of the adjunctive agent, thus permitting a lower dosage of it. Rauwolfia will also block some of the untoward effects of other drugs, an example being the blockade of the cardio-accelerator effect of hydralazine.

There are several general cautions which require consideration when undertaking combination therapy with Rauwolfia: (1) when Rauwolfia is used with either adrenergic or ganglionic blocking drugs, the Rauwolfia should be begun first. It will permit a lower dosage of the peripheral agent and thereby lessen the potential untoward effects. (2) The efficacy of Rauwolfia is not increased by giving larger doses orally than those described above. (3) All agents used in combination with Rauwolfia must be given by the titration procedure until an optimal blood pressure response is obtained. (4) Most agents used with Rauwolfia will have a predominantly orthostatic effect upon the blood pressure. It is imperative, therefore, that the dosage of the adjunctive agent be established and regulated by the upright blood pressure determination. (5) In patients who have underlying renal disease, the standing blood pressure should not be reduced below the upper limits of normal in order that renal excretory function not be damaged. (6) If adrenergic blocking agents are used in combination with Rauwolfia, care should be taken to avoid excessive hypotension for there is no effective antidote.

Rauwolfia Plus Hydralazine. This has been discussed under hydralazine. It must be remembered that Rauwolfia should be started first in order to block the hydrazaline cardio-accelerator effect. Because of the increased renal blood flow produced by hydralazine, this combination is sometimes used in patients with moderate to severe renal disease and hypertension. However, the renal effect is apparently a temporary response. The hydralazine is begun in a small dosage, 25 mg. q. i. d. and increased in a titration fashion until an optimal blood pressure reduction is obtained.

Rauwolfia Plus Veratrum. See discussion in section devoted to veratrum. It is the opinion of the authors that this is not a particularly potent or useful combination because of the untoward effects attendant to the use of oral veratrum preparations.

Rauwolfia Plus Hexamethonium, Pentolinium (Ansolysen) or Mecamylamine (Inversine). Rauwolfia with either hexamethonium, pentolinium, or mecamylamine constitutes the most potent drug combination available for treating hypertension which has thus far been reported. Hexamethonium, pentolinium and mecamylamine act at the ganglia (both sympathetic and parasympathetic). Reflexes responsible for the postural adjustment of blood pressure are blocked resulting in a predominantly orthostatic reduction of the blood pressure. Side effects (other than nasal congestion and bradycardia) are due to ganglionic blockade. Rauwolfia permits a lower dosage of the ganglionic blocking agent than would be effective if ganglionic blockade alone was used. The dose of Rauwolfia is fixed whereas the dosage of hexamethonium, pentolinium and mecamylamine is increased by titration until an optimal reduction in the upright blood pressure is obtained.

TABLE 4

COMPARISON OF BLOOD PRESSURE RESPONSE—MECAMYLAMINE, HEXAMETHONIUM AND PENTOLINIUM

	Mecamylamine		+ *Rauwolfia* + *Hexamethonium*		*Pentolinium*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Number patients treated	50	100	75	100	75	100
Responsive	46	92	57	76	59	79
Normotensive	12	24	28	37	25	33
Unresponsive	4	8	18	24	16	21
Average dose of responders	17 mg.		2307 mg.		341 mg.	

It is the authors' belief that Rauwolfia in combination with either hexamethonium, or pentolinium is equally effective in treating hypertension. Seventy-five patients received Rauwolfia plus hexamethonium for three months or more with a 76 per cent response rate. They were then shifted as a group to Rauwolfia plus pentolinium with no significant change in response rate.[50] The dosage schedule of hexamethonium and pentolinium is discussed more completely in the sections devoted to them. Because of its more complete oral administration, mecamylamine is apparently superior.

Rauwolfia Plus Phenoxybenzamine (Dibenzyline). Although phenoxybenzamine had been discarded from our clinic because of the high incidence of side reactions, it now appears that this agent in combination with Rauwolfia can be very useful in the treatment of hypertension, particularly in those patients with severe grades of hypertensive disease who are unresponsive to less potent agents. This agent can be given in approximately the same indications as hexamethonium or pentolinium (Ansolysen). Of 19 patients receiving Rauwolfia plus phenoxybenzamine, significant blood pressure response was obtained by 74 per cent. The limiting factors with this combination as with the ganglionic blocking agents, are variability of response and the fact that the maximum effectiveness is only realized in the upright position. As a result, when effective doses are used, dizziness and occasional syncope due to excessive reduction of blood pressure on standing are to be anticipated. Constipation has not been a problem with phenoxybenzamine since it does not affect the parasympathetic nervous system as the ganglionic blocking agents do.

(To be continued)

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EDITORIALS

EPIDEMIOLOGY OF INFECTIOUS MONONUCLEOSIS

Though this disease has been recognized as a clinical entity for many decades, it was not until the heterophile agglutination test was described some 25 years ago that the disease could reasonably be separated from others associated with abnormalities of the white cells. In spite of the fact that infectious mononucleosis has been under study for these years, nothing clearcut has ever been advanced which throws light on its transmission.

The studies which have been made in an attempt to transmit the disease include material from gargle washings, feces, and lymph nodes removed and ground up. All investigations have ended in failure. The disease has been transmitted by injections of blood, from donors ill with the disease but this is of no epidemiologic significance.

Although epidemics of the disease have been alleged to occur in children, some of these are open to question on clinical and serologic data. The true facts are that infectious mononucleosis is a disease seen in an overwhelming majority of instances between the ages of 17 to 25, and rarely over 40 years of age. Surely it is not a contagious disease to be ranked with the childhood diseases in ease of transmission, otherwise it would not appear in such high incidence in young adult life. Furthermore, this disease so common in the experience of student health services of universities and colleges, and of the medical officers of the armed services, has been noted to occur practically never among room-mates or other close contacts thus virtually ruling out droplet infection.

Because of these facts and his epidemiologic investigations, Hoagland,* at the U. S. Military Academy, offers his theory as to the transmission of infectious mononucleosis. First he casts doubt upon many of the "epidemics" which have been reported in the past. He points out since the heterophile test developed by Paul and Bunnell has come into common use, reported epidemics have been fewer. His reasons for suspecting the diagnosis in reported epidemics are based on one of several discrepancies. In some, even since the heterophile test has been available it was not done, or done in only a minority of the patients alleged to have the disease. In some, tests were done after overnight refrigeration, which technic is associated with many false positive results. In other "epidemics" the heterophile tests done on sample cases were not checked by guinea pig kidney absorption tests to exclude the heterophile agglutination sometimes found in normal sera.

Having considered the validity of these "epidemics," Hoagland goes on to develop his theory of the transmission of infectious mononucleosis. He first points to the report of three cases which developed on a destroyer, where the crew lives in crowded quarters for weeks on end, five weeks after a shore liberty. No other instances of the disease appeared. In his six years of study of infectious mononucleosis at the U. S. Military Academy, Hoagland has gone carefully into the epidemiology in 73 cases. Most of his cases appeared in February and August. His first case was in a cadet who became ill in February, 1951, and who had spent some hours on the train before Christmas in company with a female medical student whom he had never seen before. They engaged in intimate kissing permitting the mixing of saliva. In later correspondence it appeared that she developed the disease three days before her contact with the cadet. They both were also exposed to a bottle which was passed around among a group of train acquaintances. This cadet contact thus had an incubation period of 47 days.

In his 73 cases, Hoagland found that all except two had engaged in such intimate oral contacts 32 to 49 days before illness. Three had had only one such contact 42 to 45 days previously. Of the two without a history of kissing, one frequently drank from bottles passed to him by friends. He explains the February and August incidence in his cases by the fact that the semi-annual vacations fall some weeks before this time, which, because of the restricted life at the Academy,

*Hoagland, R. J.: The Transmission of Infectious Mononucleosis, Am. J. M. Sc. 229:262, 1955.

offers practically the only possibility of the necessary exposure. This fits the pattern of the three cases on the destroyer.

Hoagland points out that his hypothesis explains a number of facts. It explains the high incidence in the 17 to 26 year old group (he has never seen a patient under 14 and rarely one over 30 years of age in over 200 cases). It explains why the disease does not appear in room-mates or spread in a dormitory. Though infectious mononucleosis is frequent among nurses, medical students and internes there are no cross-infections among patients in the hospitals. It explains why the disease is rare among married persons, there being less promiscuous kissing.

No doubt this hypothesis of the epidemiology and transmission of infectious mononucleosis will be put to the test in student health services. With new thoughts of an extended incubation period and the probability of a virus nonviable outside the body, further studies in experimental transmission will be needed, especially to establish the possibility of a carrier state, a probability suggested by some of Hoagland's cases.

It will be interesting to await further observations by others.

EDITOR.

THE CLINICAL HISTORY

Upon reading the pertinent remarks our President made in his address upon the subject of the patient's history, the thought occurred that these comments might be expanded a bit.

For one in academic medicine to dilate upon the importance of adequate history taking means the almost certain criticism of impracticality. A busy doctor has to take short cuts, and the best place to cut the time spent on the patient is to more or less by-pass the history, or at least take an abbreviated one. Such a running argument would seem quite practical and one not to be gainsaid.

However, this clinical academician having experienced the exigencies of practice will continue to maintain that the adequate history is the mainstay of diagnosis, not surpassed by any other diagnostic technic used or available, whether the physical examination, the laboratory tests, or the special aids such as the x-ray film or the electrocardiogram. This is a general statement, and the exceptions to it make up the minority. To be sure asymptomatic rheumatic valvular disease may be a chance finding by use of the stethoscope, and the early minimal tuberculous lesion of the lung may be found by a routine chest film.

Obviously the importance and length of the *adequate* history will vary within wide limits. The history in the patient who has a fracture deformity of an extremity which meets the eye may need only a sentence or two to record how the accident occurred. The history in an instance of acute upper respiratory infection may be brief.

But when the patient's complaint is one of chronic nature, or indicative of systemic disease the history comes into its own as the main highway to diagnosis. The clinician's acumen and experience stand out boldly in his history, his clinical background being recorded in the queries made and the selection of the material set down on paper. If this statement is true there is a corollary one,—*the physician responsible for the patient can not delegate the history taking to anyone else.*

At this point comment might be made regarding the history check form and history taking by the office nurse. It may be granted that in several highly specialized fields a history check sheet may be used. In the obstetrical case the doctor is dealing in the main not with disease, but a normal physiologic process, usually in a young woman who very frequently has had an essentially negative past history. In ophthalmology only the minority of patients may have a lengthy history. Thus the history check form may be condoned in certain special circumstances. But in the case study of the chronically ill patient or one with systemic disease, the history check form is an abomination. Only a blank piece of paper offers the psychologic stimulation to record a full history and a detailed past history or system review that may have profound bearing on the present illness.

If a check sheet for a history is permissible a nurse historian is permissible. But it has already been indicated that no one can take a history for the physician who is to be responsible for the patient.

Here is his most valuable tool in diagnosis and he must perforce wield it himself. The history itself may provide the diagnosis. If

not, it may offer the necessary aid to interpret physical findings and thus lead to the diagnosis. Or, if still more objective study is needed, the history only can point to the *intelligent* use of laboratory and other diagnostic methods. The use of diagnostic aids without an adequate history is like a rudderless ship veering crazily from one point to another, devoid of a course set to find a harbor. Because of the mental laziness which leads to dependence on objective diagnostic aids, the medical profession has forfeited much of the public's respect for his astuteness and experience, and he himself has educated the public to think of him as an interpreter of reports from laboratories,—a kind of super-technician, one lacking the acumen to make a diagnosis without spending a month of the patient's salary.

The statement made that a history is often the only diagnostic resource at hand can be easily proven if one thinks of the great mass of functional or psychosomatic complaints presented to the doctor daily. Is there any method of making such a diagnosis objectively? Obviously not! To arrive at such a diagnosis by exclusion, after negative x-ray, electrocardiographic and laboratory studies is a diagnosis built on sand, for there may be serious organic disease at the basis of the complaints. The diagnosis of psychosomatic or functional disease must be a *positive* one,—by history only. So too, the history of serious disease may be on history only,—tic douloureux, syphilis, angina pectoris. None of these may be substantiated by any objective finding, physical or otherwise.

One need not recapitulate the great number of cases of disease of any of the body systems in which the history, interpreting the physical findings, establishes the diagnosis. Nor does one need recall that the history makes the decision of whether a bronchoscopy or esophagoscopy should be done even though the x-ray studies were negative. Or whether, in the face of abdominal pain, the radiologist will be asked to do a gastrointestinal series or a barium enema or an intravenous pyelogram.

Since how a patient answers a question may be more important than the content of the answer, only the doctor responsible for the patient can take the history. Can the nurse interpret for the doctor the emotional reaction in tears, flushing, blanching or a tremulous voice,—clinical signs of the patient's fears, frustrations, anger and disappointment? Only the doctor can correlate these signs with the content of the history.

And finally, unless the doctor takes the history in the case of chronic or severe systemic disease, how can he learn to know his patient, and how can the patient learn to know his doctor? All too frequently one hears the patient complaining of the number of visits made to his doctor's office without ever having had a real talk with him and of not being able to discuss his troubles freely.

In summary, it can only be reiterated that an adequate history is the basic means of diagnosis. Since there are no short cuts the busy doctor must reorganize his time to find the leisure for proper history taking in his problem cases. Unable to find the time, he must in all fairness get the patient into the hands of a doctor who will do the proper thing. Searching for aid by using the time of a technician instead of his own is a sterile process in most instances.

EDITOR

THE NEW INDEX

It is our hope that the new index for the year 1955, which appears in this issue will meet the approval of the membership.

Consultation with experienced medical and reference librarians confirmed our belief that the title index which has been used for many years in the Southern Medical Journal should be changed to another form. The type of index chosen is the subject index.

In wishing to refer to a paper the reader usually thinks in terms of subject or topic rather than the title of a paper. Therefore, a subject index should be more convenient and time saving than a title index. A subject index also will permit a more rapid scanning of what other papers may have been published during the year, which may be related to the subject of reference. This makes for greater ease in collateral reading. In a subject index, cross references are more easily handled. For example, if the reader is searching for a paper on cancer of the uterus, he will find it under "uterus" immediately; if he refers to "cancer," he will find "Cancer: See also tumors; and under organs and regions."

There is a separate Author Index. This is for the convenience of the reader who wishes to refer to the paper by Dr. Blank which he read some months before, or which he heard at a Section Meeting. The name of the first author on a paper also appears parenthetically in the subject index to aid the reader in identifying the reference with an author who may be in the reader's mind.

We feel this change in indexing was indicated and hope it will be more satisfying to the reader of the Journal after he has become accustomed to it.

EDITOR

25 YEARS AGO

The Size of the Heart in Goiter*

"The question of cardiac enlargement as the result of hyperthyroidism has long been unsettled. One gains an impression from the literature that cardiac enlargement from hypertrophy or dilatation, or both, is a frequent finding in hyperthyroidism and that it is due in some way to the disease in question. Many statements have been made without adequate statistical evidence to support them. We felt it desirable, therefore to study by Roentgen ray a consecutive series of 100 patients with hyperthyroidism and compare it with an equal number of patients with nontoxic goiter.

"In determining the size of the heart in any individual, the question of slight degree of hypertrophy or dilatation is difficult to settle. Most of the methods in present-day use for determining the size of the heart correlate the area of the frontal silhouette as determined by orthodiagraphic tracing, and the body weight or height, or both. It is obvious that in a group of patients who have lost weight, particularly when the weight loss has been excessive or the patient has been unable to estimate the weight loss, this method of determining heart size is open to question, particularly when slight enlargement is to be decided upon. We have, therefore, simply recorded the heart measurements from teleroentgenograms in a series of consecutive cases. - - -

"The radiographs of the heart in this series were taken at the usual 7-foot distance, with the patient holding his breath neither in full inspiration nor full expiration. - - -

"Heart disease may occur in patients with goiter as well as in any other group of individuals. This must be taken into consideration before ascribing cardiac enlargement to goiter. - - - In the study of any group of individuals one finds a certain number with cardiac enlargement without obvious clinical or anatomic cause. This group displaying cardiac enlargement would, in most instances, fall in the fourth to sixth decade. Without known etiology the enlargement would probably be classed clinically as myocarditis or arteriosclerotic heart disease. - - -

"The diagnosis of coincident heart disease in the presence of hyperthyroidism is frequently difficult. For this study we have classified coincident cardiovascular disease under three headings: that is, rheumatic, hypertensive and miscellaneous. (a) Under "rheumatic" were included those cases which showed unquestionable evidence of valvular disease such as mitral stenosis and aortic regurgitation, with or without a history of rheumatic fever or chorea. Others with less marked evidence, that is, mitral regurgitation, who had a history of rheumatic fever, were classified as rheumatic heart disease. Most of these have been seen since operation and the character of the murmur has not changed. (b) Hypertension was diagnosed, with the exception of 5 cases, in patients over forty years of age who showed a basal systolic blood pressure of not less than 150 mm. Hg. Other evidence was used, such as changes in the retinal or peripheral vessels. A number of these patients showed a basal diastolic pressure over 100 mm. Hg. before operation, and most of them showed it after operation. - - - Of 26 toxic cases so diagnosed 25 showed distinct and well-marked hypertension three months or more after operation. - - - (c) Under the miscellaneous group were placed those patients who showed evidence of coronary disease and angina pectoris; there was one case of pericardial effusion, one case of acute glomerular nephritis with generalized edema and enlarged cardiac shadow. A diagnosis of arteriosclerotic heart enlargement might thus be too easily accounted for and, therefore, subject to criticism. While we know that it existed, we have avoided using it. - - -

"If hyperthyroidism produces any great enlargement of the heart one might reasonably expect to find greater average measurements in a group, such as we have studied. - - - - the average transverse diameter of the heart in the toxic group exceeds the average transverse diameter of the nontoxic group by only 0.49 cm. There is no question that cardiac enlargement, as a result of thyroid toxicity, must be made on a large group and not on individual cases. One must, therefore, conclude that if hyperthyroidism causes cardiac enlargement, that is, hypertrophy or dilatation or both, it does so only to a slight degree. - - -

*Hurxthal, L. M.; Menard, O. J.; and Bogan, M. E.: The Size of the Heart in Goiter. A Teleroentgenographic Study, Am. J. M. Sc. 180:772, 1930.

"Conclusions. 1. Teleroentgenograms were made on 100 consecutive cases of toxic and 100 consecutive cases of nontoxic goiter in the Lahey Clinic.

2. No definite relationship could be found between the duration of the disease or weight loss and the size of the heart.

3. Cardiac enlargement as determined by teleroentgenography showed a fairly direct relationship to age and coincident cardiovascular disease.

4. The number of enlarged hearts of different degrees was practically the same in both toxic and nontoxic goiter.

5. If hyperthyroidism causes cardiac enlargement or hypertrophy and dilatation, it is slight."

BOOKS RECEIVED

Corticotropin. Its Pharmacologic Effects in Man and Practical Therapeutic Utilization. By Gordon B. Myers, M.D., and William Q. Wolfson, M.D., Wayne University College of Medicine and Detroit Receiving Hospital. 76 pages with figures. Detroit: Wayne University Press, 1955.

Clinical Roentgenology, Volume III. The Lungs and the Cardiovascular System Emphasizing Differential Considerations. By Alfred A. deLorimier, M.D., Radiologist, St. Francis Memorial Hospital and Consultant in Radiation Therapy for the U. S. Public Health Service at the U. S. Marine Hospital, San Francisco, Henry G. Moehring, M.D., Radiologist, Duluth Clinic and John R. Hannan, M.D., Radiologist, Lake County Memorial Hospital, Painesville, Ohio. 492 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $20.50.

Cancer Cells. By E. V. Cowdry, Director, Wernse Cancer Research Laboratory, Washington University, St. Louis. 677 pages, 137 figures. Philadelphia: W. B. Saunders Co., 1955. Price $16.00.

Mental Hygiene in Public Health. By Paul V. Lemkau, M.D., Professor of Public Health Administration, Division of Mental Hygiene, School of Hygiene and Public Health, Johns Hopkins University. Second Edition; 450 pages. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price $8.00.

Present-Day Psychology. Edited by A. A. Roback. 972 pages. New York: Philosophical Library, 1955. Price $12.00.

Atomic Energy Research at Harwell. By K. E. B. Jay, Principal Scientific Officer at Harwell. 143 pages. New York: Philosophical Library. Price $4.75.

Medical and Psychological Teamwork in the Care of the Chronically Ill. Edited by Molly Harrower, Ph.D., Research and Consulting Psychologist, New York. American Lecture Series. 227 pages. Springfield, Illinois: Charles C. Thomas, Publisher. Price $5.75.

Histamine—Its Role in Anaphylaxis and Allergy. By M. Rocha E. Silva, M.D., Department of Biochemistry and Pharmacodynamics, Institute Biologico, San Paulo, Brazil. American Lecture Series. Springfield, Illinois: Charles C. Thomas, Publisher. Price $7.50.

Splenin A in Rheumatic Fever. By Alvin F. Coburn, M.D.; Lucile V. Moore, M.D.; Judith Wood, M.D.; and Mary Roberts, R.N., from the Rheumatic Fever Research Institute, Northwestern University Medical School, Chicago. 86 pages. Springfield, Illinois: Charles C. Thomas, Publisher. Price $3.75.

The Shoulder and Environs. By James E. Bateman, M.D., F.R.C.S., Orthopaedic Consultant, Sunnybrook Hospital, Toronto. 539 pages, illustrated. St. Louis: The C. V. Mosby Company, 1955. Price $16.25.

Cardiovascular Surgery. Symposium held at Henry Ford Hospital. Edited by Conrad R. Lam, M.D., Surgeon-in-Charge, Division of Thoracic Surgery, Henry Ford Hospital. 529 pages. Philadelphia: W. B. Saunders Company, 1955. Price $12.75.

Cardiac Diagnosis. A Physiologic Approach. By Robert F. Rushmer, M.D., Associate Professor of Physiology and Biophysics, University of Washington Medical School. 429 pages, illustrated. Philadelphia: W. B. Saunders Company, 1955. Price $11.50.

Basic Surgical Skills. By Robert Tauber, M.D., Assistant Professor of Gynecology and Obstetrics, The Graduate School of Medicine, University of Pennsylvania. 73 pages. Philadelphia: W. B. Saunders Company, 1955. Price $3.75.

The Thyroid. Edited by Sidney C. Werner, M.D. 771 pages. New York: Paul B. Hoeber, Inc., 1955. Price $20.00.

Experimental Pharmacodynamics. By T. Koppanyi and A. G. Karczmar. 256 pages. Minneapolis: Burgess Publishing Company. Price $5.00.

Fourth Report of Joint FAO/WHO Expert Committee on Nutrition. Technical Report Series No. 97. Geneva: World Health Organization, 1955. Price $0.60.

Chronicle of the World Health Organization. Vol. 9, No. 8. World Health Organization, 1955. Price $0.30.

Chemotherapy of Tuberculosis. Transactions of the 14th Conference, February, 1955. Prepared and Edited by the Veterans Administration Area Medical Office, Atlanta, and the Department of Medicine and Surgery, Central Office, Washington.

INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Footnotes and bibliographies should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

Editorial Address: All manuscripts, corrected galley proof, reprint orders, books for review and related correspondence should be addressed to the Editor, R. H. Kampmeier, M.D., Vanderbilt University School of Medicine, Nashville 5, Tennessee.

Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, Empire Building, Birmingham 3, Alabama.

Office Procedures. By Paul Williamson, M.D. 412 pages, illustrated. Philadelphia: W. B. Saunders Company, 1955. Price $12.50.

Textbook of Endocrinology. Edited by Robert H. Williams, Executive Officer and Professor of Medicine, University of Washington Medical School, Seattle. 776 pages, 175 figures. Second Edition. Philadelphia: W. B. Saunders Company, 1955. Price $13.00.

Obstetrical Roentgenology. By Robert Berman, M.D. 599 pages. 386 illustrations. Philadelphia: F. A. Davis Co., 1955. Price $12.50.

Premature Infants. By Ethel C. Dunham, M.D., Formerly Associate Clinical Professor of Pediatrics, Yale University School of Medicine. Second Edition. 459 pages. New York: Paul B. Hoeber, Inc., 1955. Price $8.00.

Salivary Gland Tumors. By Donald E. Ross, M.D., Chief Surgeon, Ross-Loos Medical Group, Los Angeles. 86 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $7.50.

A Short History of Medicine. By Erwin H. Ackerknecht, M.D., Professor of History of Medicine, The University of Wisconsin Medical School. 258 pages. New York: The Ronald Press Company, 1955. Price $4.50.

Old Age in the Modern World. Report of the Third Congress of the International Association of Gerontology, London, 1954. 647 pages. Baltimore: Williams and Wilkins Company, 1955.

The Mechanisms of Healing in Human Wounds. By Shattuck W. Hartwell, M.D., Attending Surgeon, Hackley Hospital and Chief of Surgery, Mercy Hospital, Muskegon, Michigan. American Lecture Series. 166 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $4.75.

SOUTHERN MEDICAL NEWS

ARKANSAS

Dr. L. H. McDaniel, Tyronza, gave the principal address "The Heart of Medicine" at the dedication ceremony of the new headquarters building of the State Medical Society of Wisconsin, at Madison, on Saturday, October 15. Dr. McDaniel is president of the Arkansas Medical Society and past chairman of the Section on General Practice of both the American and Southern Medical Associations and a past member of the Council of the Southern Medical Association from Arkansas.

Dr. E. A. Mendelsohm, radiologist, Fort Smith, has been authorized by the Atomic Energy Commission to use Cobalt 60 Teletherapy equipment.

Dr. Paul Wright assumed direction of the Izard County Memorial Hospital at Melbourne, August 1.

Dr. B. N. Saltzman, Mountain Home, has announced the addition of eight rooms to his clinic to be completed this fall.

Dr. S. Wright Hawkins, Fort Smith, was recently elected a member of the local school board.

Dr. J. W. Ryburn, Pocahontas, was honored on the occasion of his 80th birthday by his fellow townsmen August 24. A "surprise" party with many gifts to the octogenerian was held to also celebrate his regaining his health after some months spent in a Jonesboro hospital.

Dr. Irving J. Spitzberg, Little Rock, was appointed a few weeks ago as the director of nurse training for the State of Arkansas for the Forty and Eight Grand Voiture of Arkansas by Dr. J. Lamey, the national director of nurse training for that organization.

Dr. R. B. Robins, Camden, has recently been appointed by Walter Alvarez, editor of *Modern Medicine,* to represent general practice on that publication's editorial board.

Dr. Swan B. Moss and Dr. Robert McDonald have purchased the Memorial Clinic at McGhee, and are operating it together since October 1. Dr. McDonald moved to McGhee from Eudora.

Dr. John D. Olson, Fort Smith, and Mrs. Olson have returned from a two-month trip to Europe where he attended the International Society of Surgeons in Denmark last July.

Dr. Roy E. Schirmer, Fort Smith, was made an Associate Fellow of the American College of Allergists at a recent meeting in Chicago.

DISTRICT OF COLUMBIA

Dr. James E. Fitzgerald is coordinator of a Medical Education for National Defense program at Georgetown University School of Medicine. In preparation for this appointment, Dr. Fitzgerald attended a course on "The Medical Care of Atomic Casualties" at the Walter Reed Army Medical Center in January and traveled on the Orientation Tour for Deans and MEND Coordinators in March, 1955.

New officers for the Clinical Society of the Diabetes Association of the District of Columbia are: Dr. Samuel D. Loube, president, Dr. James M. Moss, vice president, Dr. Louis K. Alpert, secretary-treasurer.

Dr. Frank W. Konzelmann is one of nine physicians recently appointed to the Medical Advisory Committee of the American Red Cross. The purpose of the committee will be to keep Red Cross workers in health and allied fields in touch with advancements in medical science.

Dr. Worth B. Daniels, clinical professor of medicine, George Washington University School of Medicine, has been elected to serve on the Armed Forces Medical Library Advisory Group for a three-year period, his term expiring on June 30, 1958.

Dr. Harold Stevens, professor of neurology at George Washington University School of Medicine, has been elected to membership in the Philadelphia Neurological Society.

Dr. Zigmond M. Lebensohn left Washington on September 10 for London, where he attended the

Third International Congress on Criminology, September 11-17. Dr. Lebensohn was gone about six weeks, visiting psychiatric centers on the continent and in Israel. He returned to Washington October 25.

FLORIDA

The new officers of the North Florida Radiological Society elected at the quarterly meeting, October 6, 1955, are as follows: Dr. Ivan Isaacs, Jacksonville, and Dr. Marvin Harlan Johnston, Jacksonville.

Dr. Curtis D. Benton, Jr., Fort Lauderdale, has been awarded a certificate of appreciation for serving as an instructor in ophthalmology at the meeting of the American Academy of Ophthalmology and Otolaryngology in Chicago, October 10-14, 1955.

Two new department heads have been appointed in the University of Florida's College of Medicine. Dr. Thomas H. Maren has been appointed professor and head of the Department of Pharmacology and Dr. Joshua L. Edwards, professor and head of the Department of Pathology. Both appointments became effective December 1.

Dr. Joshua M. Price, Live Oak, was honored by the Kiwanis Club there at a meeting held in August. Club members dedicated their meeting to him in recognition for his more than 50 years of service to the city and county.

Dr. Herman K. Moore, Key West, was principal speaker at a recent meeting of the Lions Club of Key West. He recounted some of his experiences during a month's postgraduate course at Vienna, Austria.

Dr. Wilson T. Sowder, Jacksonville, was honored September 15 by employees of the State Board of Health on his tenth anniversary as state health officer. The theme for the hour long program was "A Decade of Progress." Speakers included Dr. John D. Milton, Miami, president of the Florida Medical Association, Dr. R. A. Vonderleher, Atlanta, regional medical director, U. S. Public Health Service, and Senator Fletcher Morgan. Dr. Sowder was presented a gold watch on behalf of Board of Health employees.

GEORGIA

Dr. Edgar R. Pund, president of the Medical College of Georgia and formerly the chairman of the Department of Pathology at the Medical College of Georgia, has been appointed "Expert Consultant to the Surgeon General of the U. S. Army" for a 30 days inspection and lecture tour of the medical facilities of the U. S. Army in the Far East.

The Thomas County Medical Society elected Dr. Kirk Shepard, Thomasville, as president at a recent meeting succeeding Dr. Mervin B. Wine. Dr. Warren Taylor was named vice president and Dr. Julian Neel was re-elected secretary-treasurer.

Dr. Richard A. Dodelin, Savannah, has been awarded a March of Dimes fellowship by the National Foundation for Infantile Paralysis. Dr. Dodelin is now specializing in orthopedic surgery and is studying at Duke University, Georgia Warm Springs Foundation and cooperating institutions.

Dr. William J. McAnally, Jr., Thomasville, is the new medical director of Region III of the U. S. Public Health Service. Dr. McAnally is taking over the job of Dr. M. M. Van Sandt who has been reassigned.

Dr. Wray J. Tomlinson, Jacksonville, Florida, has accepted the appointment as pathologist of the Columbus City Hospital. He will replace Dr. A. Ralph Monaco who resigned recently.

Dr. Roger W. Dickson, Atlanta, has recently been appointed senior civilian consultant in pediatrics for the Third Army.

Dr. Marion B. Hines, professor of anatomy at Emory University, has been invited to deliver a series of lectures at Cambridge University in England this fall. Dr. Hines will address Cambridge anatomy students on the structure and function of the cerebral cortex in primates. She has studied at Cambridge University College in London, and the University of Wurzburg (Germany). She also holds the Ph.D. degree from the University of Chicago.

Dr. John M. Howard, former head of a medical research team in Korea, has been named chairman of the Department of Surgery and Joseph Brown Whitehead professor of surgery in the Emory University School of Medicine. Dr. Howard is a native of Selma, Alabama.

Dr. J. Willis Hurst, formerly of Emory University, has recently made the front page of many papers. Dr. Hurst, who is near the end of a tour of duty with the U. S. Navy as a lieutenant commander at Bethesda Naval Hospital, was the attending physician to Senator Lyndon Johnson, Senate majority leader, when he suffered a heart attack some weeks ago.

Dr. David Henry Poer, Atlanta, has been named a member of the medical advisory board of the Sears-Roebuck Foundation. Function of the board is to assist the Sears-Roebuck Foundation in the development and administration of programs of interest to the medical profession.

Dr. Paul L. Reith, Atlanta, has been appointed director of orthopedic surgery at the Warm Springs Foundation. He assumed his duties on October 1. Dr. Reith succeeds Dr. Edwin Erwin who resigned to enter private practice.

Dr. H. B. Jones, Gray, has been invited to join the staff of the Macon Hospital. He is the first physician living outside Bibb County to be asked to be a staff member. In addition to his office in Gray, Dr. Jones also has an office and clinic in Monticello.

Dr. J. N. Stribling, Eatonton, has been made a technical advisor on the health board for the Georgia Department of Civilian Defense.

Two new fields of service have been set up at Macon Hospital, plastic surgery and thoracic surgery. Dr. J. P. Woodhall was named chief of thoracic surgery, and Dr. W. H. Holden was named chief of plastic surgery.

Dr. J. C. Dover, Clayton, who has doctored Rabun Countians for over 50 years, was honored on August 26 with a "Dr. Dover Birthday Party." Approximately 300 people attended the dinner party which celebrated the physician's 80th birthday.

Continued on page 50

BOOK REVIEWS

The Mask of Sanity

By Hervey Cleckley, M.D., Professor of Psychiatry and Neurology, Medical College of Georgia. 3rd Edition. 585 pages. St. Louis: The C. V. Mosby Company, 1955. Price $9.50.

This work is the third edition of Dr. Cleckley's volume devoted to the problem of the so-called psychopathic personality. The basic postulate of this book is that the psychopath of the type described is suffering from an impairment of his ability to adjust socially and emotionally to his environment to the extent that he should be considered psychotic and incompetent and in need of treatment or close supervision. The author further explains his concept of the semantic disorder in this condition. By this term he refers to the distortion of the inner affective experience of the psychopath with the outward, superficial appearance of the personality seemingly intact. It seems that this concept might be summarized by the term "emotional aphasia." Dr. Cleckley points out the need for special facilities other than those now available for treatment of this disorder.

Few changes have been made since the second edition. Recognition of the revised standard nomenclature for character and personality disorders is given but does not appear to be integrated into the subject matter of the volume. The case histories have not been changed. They remain very vivid descriptions of the extreme psychopath and constitute about one-half of the book. The sixteen points which are given as characteristics of the psychopath are discussed in individual chapters as before.

From the point of clinical description of the psychopath, this book is excellent and makes for interesting reading. Dr. Cleckley's point regarding the incompetency of the extreme of this type of personality is well made. The dynamics of personality development in the etiology of the psychopath, however, appear underemphasized. This book can be recommended primarily as an interesting clinical description of that extreme group of character disorders sometimes referred to as "the old-fashioned psychopath."

Neurochemistry

The Chemical Dynamics of Brain and Nerve. Edited by K. A. C. Elliott, Ph.D.; Irvine H. Page, M.D., and J. H. Quastel, Ph.D. 900 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $19.50.

The chemistry of the central nervous system has been too long neglected and too obscure. A whole book of nearly a thousand pages about it is a welcome sight. Since it was unlikely any one person would contribute as well as a group of specialists the book is a compilation of articles by 32 individuals. The topics range from the history of knowledge of chemistry of the brain, and its founder, Thudichum, through metabolic phenomena of all types, enzymes and humoral substances, the relation of circulation and nutrition to the nervous system, pathology, toxins, the increasingly important nucleic acids, and even a short attempt at interpreting the actual function of the brain in conveying messages. More topics than can be mentioned are covered.

There is much sound data here interpreted by the respective specialists and supplied with ample specific references and bibliography for the reader who wishes further detail. This is the future source book for many types of investigators who will want information related to the biochemistry and metabolism of the brain. No doubt it will be used by people in varied disciplines and perhaps by more of those not in chemical fields—because of the wideness of coverage. For example there are 70 pages on the physiological significance of acetyecholine with nine additional pages of references. There is ample treatment of the drugs which have special affinity for nerve cells only, and studies on convulsive activity of drugs. The comparative side is not overlooked since the nervous system of arthropods is considered with its contribution particularly to the effects of toxins, such as DDT, and so forth. Information on so many items related to the chemistry of the nervous system is buried in articles never read by the neurologist or neurophysiologist that this book which collects, interprets and condenses the information should prove valuable to many in those fields as well as to chemists and pharmacologists. It is a book to own and not to borrow.

Essentials of Biological and Medical Physics

By Ralph W. Stacy, Ph.D., Associate Professor, Laboratory of Biophysics, Department of Physiology, Ohio State University; David T. Williams, Ph.D., Physicist, Battelle Memorial Institute, Columbus, Ohio; Ralph E. Worden, M.D., Associate Professor, Physical Medicine and Rehabilitation, College of Medicine, Ohio State University; and Rex O. McMorris, M.D., Associate Professor and Chairman, Department of Physical Medicine and Rehabilitation, University of Louisville Medical School. 586 pages. New York: McGraw-Hill Book Company, Inc., 1955. Price $8.50.

The purpose of this book as stated by the authors in the preface is that it may serve as a textbook for students in a course in biophysics. It is divided into 11 parts which include, for example, sections on Mechanical Biophysical Systems (physical properties of bone and muscle), Bioacoustics, Biophysical Studies Involving Light, Gas Physics in Biology, Fluid Flow Systems, Heat and Thermodynamics in Life, Electrical Systems in Biology, and Nuclear Physics in Biology. As indicated by the authors, this text is not intended to be used as an advanced reference. For this reason complete explanations of certain phenomena are omitted and reference made to pertinent original articles. The physical theory and equations that are presented, however, seem detailed enough to require more than the average amount of background in physics obtained by medical or biology students,—

two of the three groups for which the text is intended. Clinical applications of the text material are presented throughout. The information collected in this volume represents considerable effort by the authors in critical evaluation of current literature in the areas covered. On the whole it is thorough, well organized, and should prove useful to those teaching biophysics where the background of the students is adequate. It is also recommended to those in teaching and research in related fields as a convenient and current description of the new area of biophysics.

The Halogenated Aliphatic, Olefinic, Cyclic, Aromatic, and Aliphatic-Aromatic Hydrocarbons Including the Halogenated Insecticides, Their Toxicity and Potential Dangers

By W. F. von Oettingen, M.D., National Institutes of Health. 430 pages. U. S. Department of Health, Education, and Welfare, Public Health Service publication No. 414. U. S. Government Printing Office, 1955. Price $2.50.

There has been compiled in this volume the knowledge regarding toxicity and potential dangers of the chlorine, bromine, iodine and fluorine derivatives of aliphatic and aromatic hydrocarbons which are of medical and industrial importance. Discussion of each compound includes the chemistry, analytical procedures for determination in air and biological materials, pharmacological and toxicological properties, potential uses and permissible levels for exposure, and treatment of humans poisoned by the chemicals.

The literature related to the toxicology of the halogenated hydrocarbons has been thoroughly reviewed and references included for each material discussed. Emphasis has been placed on the knowledge gained from toxicological investigations using laboratory animals, but pertinent information from clinical data has also been included.

Compounds are indexed under both their chemical and commercial names, which increases the usefulness of this volume as a reference book for persons with only occasional need for toxicological information.

This volume should be of value to workers in the fields of medicine and research where halogenated hydrocarbons may be used. Through the knowledge given it should facilitate diagnosis and treatment of poisoning by these compounds.

A Therapeutic Index

By C. M. Miller, M.D., M.R.C.P., Consultant Physician, Sefton General Hospital, Liverpool, and B. K. Ellenbogen, M.D., M.R.C.P., Sentor Medical Registrar, Royal Southern Hospital, Liverpool. 146 pages. Baltimore: The Williams and Wilkins Co., 1955. Price $3.75.

This small book constitutes a ready reference on the therapy of common disorders. It is designed for use by the recent medical graduate, and should be especially valuable to the less experienced physician working on an emergency room service. The therapeutic agents are mostly those official in Great Britain (B.P., B.P.C.). The physician educated in the United States might find the use of British names for drugs a little confusing but this should not be any major handicap to its use. The therapeutic procedures and drugs selected for inclusion have been carefully chosen. A large amount of useful information has been concentrated in a very usable and concise form.

The Pharmacopeia of the United States of America

Fifteenth Revision. Prepared by the Committee of Revision. (Official December 15, 1955). 1230 pages. Easton, Pa.: Mack Publishing Co., Distributor. Price $10.00.

U.S.P. XV. An extensixe revision of U.S.P. **XIV** has been made. One hundred sixty-three preparations included in U.S.P. **XIV** have been withdrawn and approximately 240 new preparations have been included. These changes represent not only deletion and inclusion of medical agents but also represent a current evaluation of the most suitable preparations of older effective therapeutic agents. This monograph includes very excellent chapters on general tests, processes, and apparata. These have been thoroughly revised and are presented in lucid concise manner. The currently accepted assay procedures are given in explicit detail. This volume maintains the high standard for which the U.S.P. is so well known.

Evaluation in Mental Health

A Review of the Problem of Evaluating Mental Health Activities. Report of the Subcommittee on Evaluation of Mental Health Activities, Community Services Committee, National Advisory Mental Health Council. Public Health Service Publication No. 413. Bethesda, Maryland: Department of Health, Education, and Welfare, National Institutes of Health, 1955. (Order from: Superintendent of Documents, Government Printing Office, Washington 25, D. C.) Price $2.00.

This publication of the U. S. Public Health Service undertakes a very difficult task in attempting to evaluate mental health activities. The evaluation of such problems faces intrinsic difficulties. The Subcommittee of the National Advisory Mental Health Council has been conscious of those problems and has utilized a broad, up-to-date approach, recognizing the great needs in the field. They emphasize the importance of interpersonal relationships in dealing with mental health activities. They are not only aware of the emotional impacts of the doctor-patient relationship, but also the influence of different professional groups working together is recognized. This is one of the areas where unexpected difficulties might develop and it is essential to anticipate such problems before they actually develop.

Another valuable point of discussion is that the realization of the mental health problem is often oversimplified. They point out the difficulties in evaluating actual changes of attitudes through questionnaires. Such methods are of very limited value and indicate more of what people recognize should be done, rather than what they are doing.

The problem of lay education is discussed, taking into consideration the vastness of the program and the difficulties in mustering sufficient personnel for community-wide activities. The question is raised whether it would not be better to focus attention on a few selected groups, rather than attempting to reach everyone.

The valuable volume is closed with a broad review of the literature, each item of the reference list being summarized. This publication should be of very definite value to almost anyone dealing with mental health activities and the physician, in particular, should find a great deal of helpful material.

1955 Medical Progress

A Review of Medical Advances During 1954. By various contributors. Edited by Morris Fishbein, M.D. 346 pages. New York: McGraw-Hill Book Company, Inc., The Blakiston Division, 1955. Price $5.00.

The purpose of this chronicle of the year's medical progress is stated in Dr. Fishbeins' preface. "The book which recapitulates the progress of the past offers firm ground from which to take off for a flight into the future."

The ground offered for this take off is certainly most sketchy. An attempt has been made, however, to cover all the various fields of interest. Several advances were omitted; such as the use of gastric Papanicolaou smears obtained by chemical or physical abrasions, and the presence of a newly recognized entity, chronic interstitial pulmonary fibrosis.

The repetition present is understandable, and not at all objectionable. It is hoped that the various bibliographies following some sections can be reviesd in the future to conform with the format advocated by the Editorial Section of the A. M. A.

The section on Liver Disease by Popper and Schaffner, and that covering Endocrinology written by Hurxthal and Parker, are both highlights of this volume. This volume is recommended for those who desire to obtain quickly, in capsule form, a listing of the past years advances.

Treatment in Psychiatry

By Oskar Diethelm, M.D., Professor of Psychiatry, Cornell University Medical College. Third Edition. 545 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $9.50.

This is the third edition of a very successful volume on "Treatment in Psychiatry." As the author stated in the first edition, his theory is "based on the teachings and methods of treatment of Dr. Adolph Meyer." Dr. Diethelm has used an eclectic approach to psychiatry, being basically psychobiologically oriented. He expresses considerable reservation to other approaches, particularly psychoanalytical concepts. In his section on "Treatment in General" his statements enable the reader to arrive at various interpretations and the author suggests the judicial use of advice in his treatment approach. He advocates a restricted acceptance of the concept of the unconscious and favors an evaluation of the patient's personality assets. The problem of such evaluations and value judgments has given rise to a great deal of controversy in psychiatry. Many therapists feel that a more objective therapeutic attitude is advisable, avoiding an evaluation of the patient's attitudes. The underlying motivation of behavior is considered more essential.

Dr. Diethelm advocates reassurance, re-education and "formation of better habits" in his treatment approach.

The great value of this book is the very excellent discussions of additional treatment methods utilized in modern psychiatry. The author gives a fair and clear evaluation of the different schools of psychiatry starting from orthodox psychoanalysis and its modifications to a discussion of the physical treatments. Those discussions should be very helpful to the reader in forming a clear idea of modern psychiatric treatment.

In general the book advocates a conservative approach to therapy, pointing out the various indications and contraindications for drug therapy, avoiding the dangerous overenthusiasm which has been so prevalent during the last year or two.

This book should be of great value to the discriminating reader who wants to form his own opinions as to the various treatment methods in psychiatry. It should be of value to the non-psychiatrist and to the psychiatric resident alike.

Ciba Foundation Colloquia on Ageing—General Aspects

Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch. and Margaret P. Cameron, M.A., A.B.L.S. Assisted by Joan Etherington. Volume 1. 255 pages, illustrated. Boston: Little, Brown and Company, 1955. Price $6.75.

Through the financial support of the drug and pharmaceutical firm Ciba, Ltd. of Switzerland, the Ciba foundation has been able to promote approximately thirty international symposia. These are held in London and are attended by world eminent authorities in the various fields studied.

The present volume, Colloquia in Ageing, is the first of what is anticipated to be a series. It is a transcript of the intimate dayslong meetings presided over by Professor R. E. Turnbridge of the Department of Medicine of Leeds University.

The formal presentation covers the biological, hereditary, chemical, experimental, and pathologic aspects of ageing. The round table discussions following each are quite fascinating.

The mental changes of ageing were studied, and it was pointed out that the elderly person has his greatest difficulty in undertaking a new program or activity. The effect of ageing on pulmonary function is interestingly presented. Experimental studies showed the loss of elasticity of pulmonary parenchyma with age, leading to decrease in the vital capacity and oxygenation, and increase in the lung volume. Thus showing how a certain degree of emphysema must be accepted as normal in elderly persons.

The bones, elastic tissue, reproductive systems, and the adrenalpituitary axis are discussed in relation to ageing. The effect of nutrition in youth was explored. There was presented the interesting speculation that over-feeding tended to lead to early body and sexual maturation, which in turn would lead to a shortened longevity. This idea stemmed from work done many years ago with rats which showed that malnutrition before maturation seemed to effect a prolongation of the life span, whereas employment of such malnutrition after maturation had no effect on the life span. Perhaps we are not doing our infants a true service when we feed them sufficiently to become plump. They then tend to mature earlier and may thus pay the penalty with a shorter life span.

Much of the Colloquia was concerned with the proper definition of ageing. Many definitions were presented—one of the shortest and most striking was given by Professor Franklin, a London physiologist who considered that "ageing is death taking small bites."

As can be noted this Colloquia is on an extremely theoretical plane. No immediate clinical benefits in the care of the aged patients are presented.

Handbook of Pediatrics

By Henry K. Silver, M.D., Associate Professor of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; C. Henry Kempe, M.D., Assistant Professor of Pediatrics, University of California School of Medicine, San Francisco, California; and Henry B. Bruyn, M.D., Assistant Professor of Pediatrics and Medicine, University of California School of Medicine, San Francisco, California; Assistant Clinical Professor of Pediatrics, Stanford University Medical School, San Francisco, California. 548 pages. Los Altos, California: Lange Medical Publications, 1955. Price $3.00.

This small volume which will fit easily into a house officer's pocket or practitioner's diagnostic bag is an amazing compilation of facts and figures pertaining to every phase of pediatrics. It is carefully edited by three young men whose interest and training has been broad and it should appeal particularly to medical students, interns, residents and the young practitioners who are "boning" for their Boards. It certainly cannot be recommended as a textbook but rather as a ready reference when one wishes to refresh his memory concerning such varied things as 17-ketosteroids in the 6 to 8 year age group or to review the type and pathogenesis of precocious isosexual development or the content of and the possible antidote for Sani-Flush. The volume has an attractive foremat and is well indexed.

The Spine. A Radiological Text and Atlas

By Bernard S. Epstein, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, N. Y. 526 pages, 721 Illustrations on 331 Figures. Philadelphia: Lea and Febiger, 1955. Price $16.50.

Dr. Epstein has written a good book and a handy reference book on the spine for the radiologist. It deals with all the congenital deformities, developmental malformations and trauma to the spinal column, as well as a wide variety of diseases which involve the spine and the spinal cord.

Beginning with the embryology and development of the normal spine, the author describes the normal spine from the anatomical, functional and radiographic aspects. The ten chapters deal with diseases of different types and origins, such as neoplasms, inflammatory lesions, endocrine and metabolic disorders, etc. The written material is comprehensively yet concisely presented. The reviewer particularly enjoyed inclusion of the many variations manifested by certain entities, along with the usual "typical or textbook pictures." Different theories and opinions of pathogenesis of various conditions are also advantageous.

Diseases of the spinal cord and its membranes and of the intervertebral discs are described; particularly in these sections is the application of myelography (and seldom used discography) especially stressed.

In general, a correlation is made of the bone diseases which affect the spine and other skeletal parts. The statistical frequency of spinal involvement in certain skeletal diseases is listed from the reported literature.

The volume is liberally illustrated and, in general, the illustrations are good. There are some in which the author and reader might desire improvement, but the written explanations with each picture are good and helpful. An excellent working bibliography is a valuable part of this book. No radiographic technic is included.

The reviewer recommends this well organized volume to all who are interested in roentgen diagnosis of the vertebral column and the spinal cord.

Genetica Medica. Primum Symposium Internationale Geneticae Medicae

Edited by Luigi Gedda, Direttore dell'Istituto Gregorio Mendel. 467 pages, illustrated. Roma: Istituto Gregorio Mendel, 1954. Price L.5,000.

This symposium contains 30 papers on medical genetics delivered in 1953 on the occasion of the establishment of the Gregor Mendel Institute in Rome. It was sponsored by the Italian Society of Medical Genetics and the journal *Acta Geneticae Medicae et Gemellologiae*, of which Professor Gedda is editor. A wide variety of topics are covered, including a number of comprehensive reviews. The scope of the advancing knowledge of medical genetics is well illustrated. Language difficulties will prevent wide readership: Five papers are in English, two in French, seven in German, and 16 in Italian. However, most have English summaries. An address by Pope Pius XII is presented in all four languages.

Perinatal Mortality in New York City

By Schuyler G. Kohl, M.D. Published for the Commonwealth Fund. 112 pages. Cambridge, Mass.: Harvard University Press, 1955. Price $2.50.

An intensive study was made of 955 perinatal deaths randomly selected from (A) stillbirths, (B) neonatal deaths in the first five days of life, and (C) neonatal deaths from the sixth to thirtieth day of age reported in New York City during 1950 and early 1951. Cases included were those where weeks of gestation were 28 or over and birth weight was 1,000 grams or over.

"The purposes of the study are: (1) to determine, as accurately as possible, the causes of perinatal mortality; (2) to determine the extent of preventability of perinatal deaths; and (3) to supply additional pertinent information concerning perinatal mortality, which cannot be collected by the usual vital statistics records. These additional data include such information as:

(a) Prenatal care; (b) medical care; (c) analgesia and anesthesia; (d) past obstetrical history; and (e) detailed pathologic findings."

A special staff of physicians completed the obstetrical, pediatric, and pathological records. Panels consisting of an obstetrician, a pediatrician, and a path-

ologist reviewed records for cause of death, factors of preventability, and factors of responsibility. Material was carefully reviewed a second time before publication.

Of special interest are Chapter II on preventability and responsibility factors, showing an over-all percentage of "preventability" of 35 per cent, and Chapter VIII on cause of death.

Studies of this kind should be most valuable in pointing out the possibility of, and the way toward further reduction in perinatal mortality.

The Mayo Clinic

By Lucy Wilder. 69 pages. Second Edition. Springfield, Illinois: Charles C. Thomas, Publisher, 1955. Price $3.75.

The author of this book is the wife of one of the former heads of the medical department at the Clinic. It is a short, interesting account of the origin of the Mayo Clinic, its growth, and thoughts of the future. The energy and enthusiasm of the brothers Mayo is well brought out, as are the many facets of the Clinic. There is outlined the training program in graduate education, the Mayo Foundation and its contributions in research and training. This small volume is readable and interesting for both layman and doctor. The marginal sketches by Ruth Barney, a patient "going through" the Clinic, show with humor the patients awaiting their turn in the line and other aspects of the clinic.

Everything and the Kitchen Sink

How the first century of industry created our first century of good living. Written under the general supervision of Russell G. Creviston. 160 pages, illustrated. By Farrar, Straus & Cudahy, Inc., New York. Chicago and New York: The Philip Lesly Company, 1955. Price $4.00.

This is an interesting nonmedical book, which through the medium of old prints and newer photographs provides an illustrated record of the changes in American life in the present century. It is published on the Centennial of the Crane Company. The object is to show the remarkable advances made by industry, and thereby the provision of the things that have made the American Way of Life a remarkable one in one short century in terms of comforts and standard of living.

Clinical Toxicology

By Clinton H. Thienes, M.D., Visiting professor of Pharmacology and Toxicology, School of Medicine, University of Southern California, and Thomas J. Haley, Ph.D., Associate Clinical Professor of Medicine (Industrial Medicine) School of Medicine, University of California. Third Edition. 457 pages, illustrated. Philadelphia: Lea and Febiger, 1955. Price $6.50.

There is no essential change in the presentation of the material from previous editions. New poisonous agents included are chlorinated hydrocarbon and organic phosphate insecticides, antihistaminics, antabuse, beryllium, iron, sulfur dioxide, formaldehyde, fluoro acetate, and the new curareform drugs. It is unfortunate that no chapter is included covering the general principles of handling the patient who has been subjected to a toxic agent Practitioners of medicine, clinical pathologists as well as other specialists who come in contact with problems in toxicology should find this a useful reference.

Airborne Contagion and Air Hygiene

An Ecological Study of Droplet Infections. By William Firth Wells, the Laboratory for the Study of Airborne Infection, University of Pennsylvania School of Medicine. 423 pages, illustrated. Cambridge, Massachusetts: Harvard University Press, Published for The Commonwealth Fund, 1955. Price: $6.00.

To attempt a review of this really magnificent book one should be better qualified than this reviewer. However, since very few persons possess the detailed knowledge necessary to evaluate critically this type of work there may be some excuse for a relatively unqualified reviewer to do so.

Much of the monograph deals with contributions of the Laboratories for the Study of Airborne Infection at the Harvard School of Public Health. The material is presented in two parts, one in which the principles of airborne contagion are outlined, and the second in which the habits of people which make them accessible to airborne parasites are considered. One marvels at the intricate laboratory experiments set up to test hypotheses relating to droplets and droplet nuclei. Infinitely more complex are the experiments set up in nature, these too have been studied intimately so that any criticism which argues that these experiments are in the main academic and do not apply to naturally occurring infections in human populations is not tenable. Of course, much remains to be done concerning studies of airborne infections but in this book can be found extensive observations of many of the questions which plague the clinical epidemiologist.

The book is generously illustrated and there is an extensive bibliography. It is not one which can be skimmed over lightly or just perused; in order to be appreciated it has to be studied carefully. The idea of airborne contagion through the medium of droplet nuclei is extensively developed and this reasoning applies to many of the most prevalent and damaging infections of man. The control of airborne contagion through ventilation which includes not only the circulation of air but also air disinfection by bactericidal aerosols and ultra violet irradiation is an important part of the theme of air hygiene. Air hygiene therefore includes not only the physics of atomization, the physics and physical chemistry of atomized droplets, the biology, biophysics, and biochemistry of various parasites suspended in the nuclei of droplets atomized into the atmosphere but also the physiology of inhalation of particulate matter and the parasitology of inhaled contagium.

This book should be required reading for all interested in contagious diseases and parts of it certainly should be offered to medical and nursing students to help their understanding of the difficult problem of transmission of disease.

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BIRMINGHAM, ALABAMA

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Dr. A. M. Hendrix has been elected to the City Council of Canton.

Seven new department heads have been named for the new Eugene Talmadge Memorial Hospital in Augusta, each is also a department chairman at the Medical College of Georgia and a full professor. The physicians and their departments are as follows: Dr. V. P. Sydenstricker, medicine; Dr. John Caldwell, psychiatry; Dr. William Moreta, surgery; Dr. H. B. O'Rear, pediatrics; Dr. Leland Stoddard, pathology; Dr. L. P. Holmes, radiology; and Dr. Richard G. Torpin, obstetrics. The hospital is scheduled to go into full operation about January 1, 1956.

KENTUCKY

Eight new members of the Board of Consultants on Scientific Articles for the Journal of the Kentucky State Medical Association were elected recently by the advisory committee to the editor and approved by the editor to replace retiring members, who finished a three-year term on July 1. The newly appointed consultants who will serve for the next three years are: Dr. Harry D. Abell, Paducah, Dr. Henry B. Asman, Louisville, Dr. Marion F. Beard, Louisville, Dr. Rankin Blount, Lexington, Dr. Glenn Bryant, Louisville, Dr. William C. Buschemeyer, Louisville, Dr. Richard Elliott, Lexington, Dr. Douglas Scott, Lexington.

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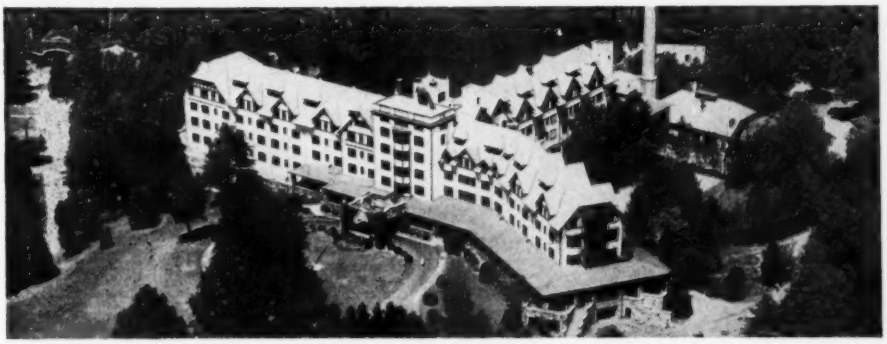

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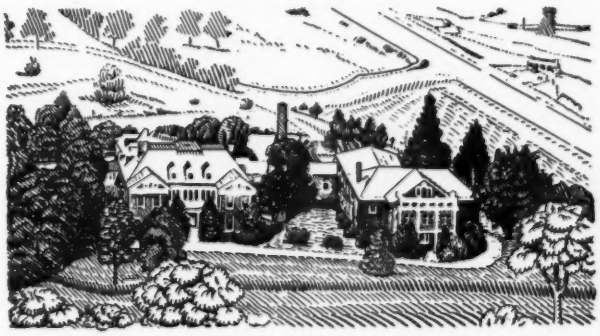

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Q4

Continued from page 50

Dr. Ernest C. Strode, Lexington, has been named chairman of the committee whose purpose it is to select the recipients of the Distinguished Service Award and the Outstanding General Practitioner Award.

Five Kentucky State Medical Association members who are on the newly appointed Governor's Committee on Rehabilitation are as follows: Dr. J. Gant Gaither, Hopkinsville, president-elect of K. S. M. A.; Dr. J. Murray Kinsman, Louisville, dean of the University of Louisville School of Medicine; Dr. Franklin Moosnick, and Dr. Marshall Jones, both of Lexington; Dr. Asa Barnes, Louisville, who also serves as an alternate on the executive committee. Dr. Elvis Stahr, Lexington, is chairman.

Dr. W. F. Carter, Pleasureville, was honored recently by the citizens of Pleasureville and the surrounding countryside for 33 years of service to the community.

Dr. Leslie Richey, Park City, was honored recently when the citizens of his community celebrated a "Dr. Richey Day," sponsored by the Lions Club of Park City. Dr. Richey has practiced for 43 years in that community.

Dr. Spafford Ackerly, Louisville, has been honored by having a society named for him. Dr. Theodore Schramm, Louisville, president of the newly formed "Ackerly Society of Psychiatric Residents of the University of Louisville School of Medicine," said its

Continued on page 56

CITY VIEW

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For the diagnosis and treatment of nervous and mental disorders, and addictions to alcohol and drugs.

Established 1907

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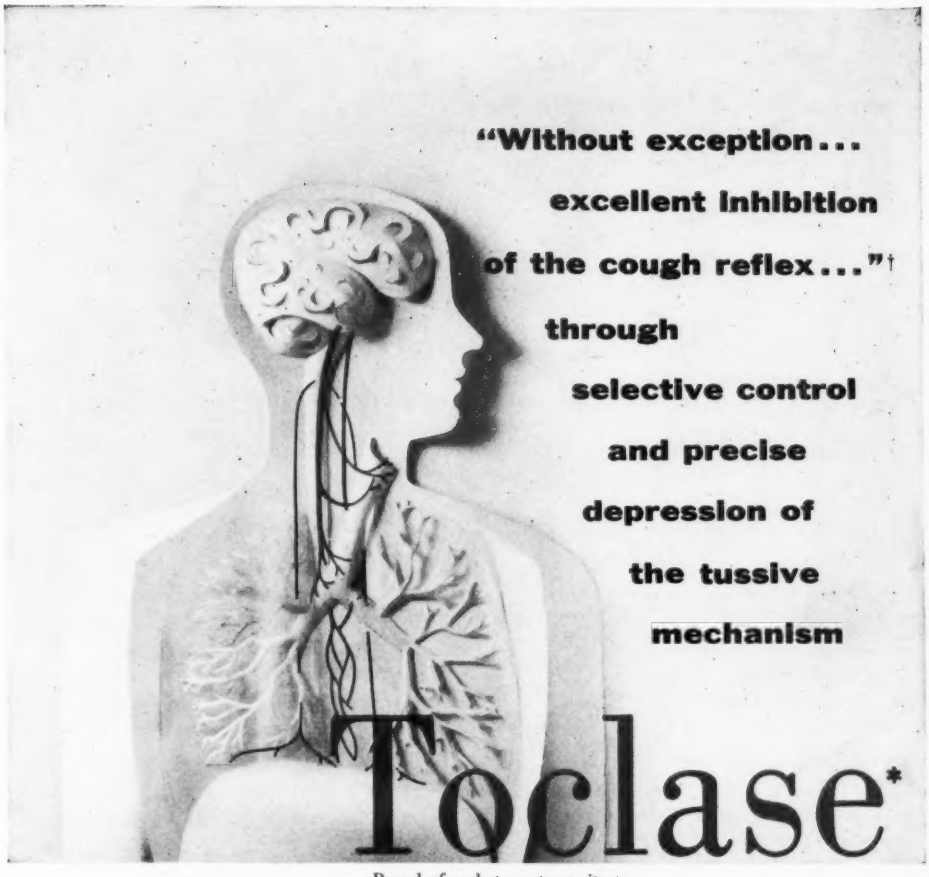

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TOCLASE EXPECTORANT COMPOUND Reduces the frequency and intensity of unnecessary cough . . . moderates, but does not abolish purposeful, productive cough. Sugar free. Pleasant-tasting, cherry-flavored, amber color syrup. Bottles of one pint.

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†Parish, F. A.: M. Times 83:870 (Sept.) 1955.

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ANNOUNCING

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of

THE NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

Conference Headquarters—Municipal Auditorium

FEBRUARY 27, 28, 29 and MARCH 1, 1956

GUEST SPEAKERS

Philip D. Woodbridge, M.D., Greenfield, Mass.
Anesthesiology

J. Lowry Miller, M.D., New York, N. Y.
Dermatology

Franz J. Ingelfinger, M.D., Boston, Mass.
Gastroenterology

John I. Brewer, M.D., Chicago, Ill.
Gynecology

S. Gilbert Blount, Jr., M.D., Denver, Colo.
Internal Medicine

Eugene A. Stead, Jr., M.D., Durham, N. C.
Internal Medicine

John H. Talbott, M.D., Buffalo, N. Y.
Internal Medicine

Lawrence S. Kubie, M.D., New York, N. Y.
Neuropsychiatry

Duncan E. Reid, M.D., Boston, Mass.
Obstetrics

Frank W. Newell, M.D., Chicago, Ill.
Ophthalmology

Claude N. Lambert, M.D., Chicago, Ill.
Orthopedic Surgery

A. C. Hilding, M.D., Duluth, Minn.
Otolaryngology

Alan R. Moritz, M.D., Cleveland, Ohio
Pathology

Joseph A. Johnston, M.D., Detroit, Mich.
Pediatrics

Philip J. Hodes, M.D., Philadelphia, Pa.
Radiology

Arthur H. Blakemore, M.D., New York, N. Y.
Surgery

Charles G. Child, III, M.D., Boston, Mass.
Surgery

Rubin H. Flocks, M.D., Iowa City, Iowa
Urology

Lectures, symposia, clinicopathologic conferences, round-table luncheons, color television, medical motion pictures, and technical exhibits.

(All-inclusive registration fee — $20.00)

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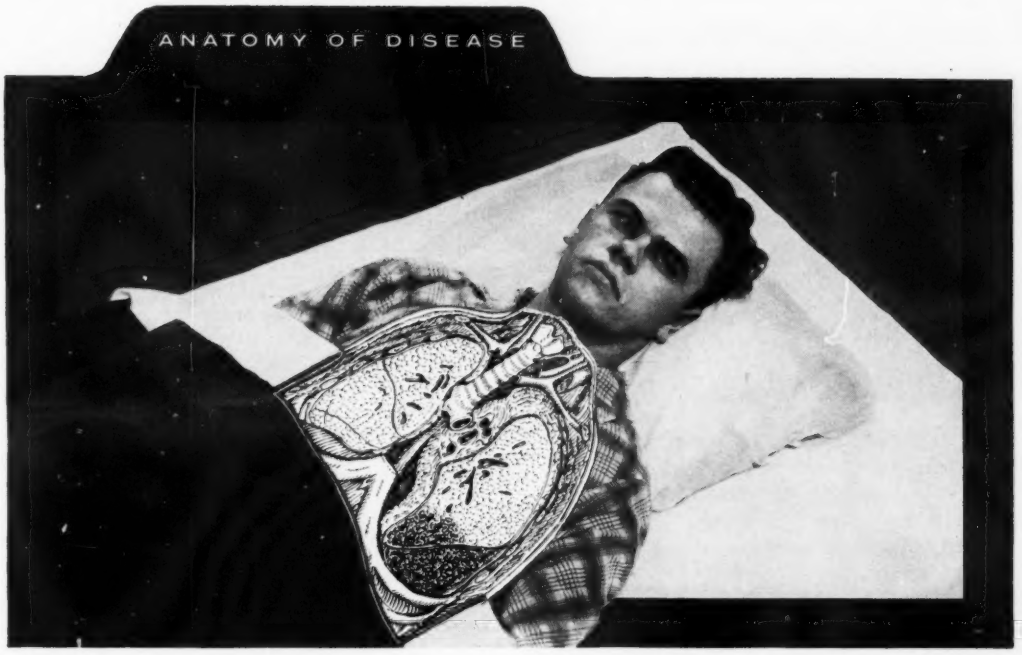
Departure from New Orleans, March 2

For Information concerning the Assembly meeting and the tour write Secretary, Room 103, 1430 Tulane Avenue, New Orleans 12, La.



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Sulfamerazine	0.167 Gm.
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Tablets:
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CHOLOGESTIN is prescribed in a dosage of 1 tablespoonful in cold water after meals. Three tablets of TABLOGESTIN are equivalent to 1 tablespoonful of CHOLOGESTIN.

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Please send me free sample of TABLOGESTIN together with literature on CHOLOGESTIN.

DR.....

STREET.....

CITY.....ZONE.... STATE.....

Continued from page 52

purpose was the exchange of ideas on different aspects of psychiatry.

Dr. Frank M. Gaines, Jr., Kentucky Commissioner of Mental Health, was elected chairman of a 16-state Southern Regional Council on Mental Health Training and Research at the organization of the council in Atlanta, Georgia, on July 12.

Dr. Charles B. Stacy, Pineville, has returned to the states following a two-month tour abroad. His travels carried him through Europe and Africa.

Dr. John Leslie Vogel has become associated with Dr. Arthur Clayton McCarty in the practice of internal medicine at Louisville. Dr. Vogel graduated from Duke University in 1950 and served his internship at Grady Memorial Hospital, Atlanta, Georgia, in 1950-51.

Dr. J. W. York, Cammer, announced his retirement from the practice of medicine in June, due to the ill health of his wife. He graduated from the University of Nashville Medical Department in 1909.

Dr. G. M. Gumbert, Jr., gave up his practice at Olive Hill to take some additional surgical training at the Good Samaritan Hospital, Lexington, last July 1.

Dr. Roy Mason Kash has opened offices again at Mt. Sterling where he was located prior to taking special courses in diseases of the eye, ear, nose and throat at the University of Louisville and the Barnes Hospital in St. Louis.

Continued on page 58

TULANE UNIVERSITY

SCHOOL OF MEDICINE

DIVISION OF GRADUATE MEDICINE

Ocular Pathology	Dec. 5-9, 1955
Fluid and Electrolyte Balance	Jan. 16-21, 1956
Pediatric Neurology	Feb. 27-March 3, 1956
Industrial Medicine	Apr. 12-13, 1956

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glucuronic acid encourages repair of connective and fibrous tissue.

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glucuronolactone 2½ grs.,
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for improved nutritional status... clinical response

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Betaine Hydrochloride . . . . . 130.0 mg.
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Surrounding an enteric-coated core of:
Pancreatin (4 x U.S.P.) . . . . . 62.5 mg.
(Equiv. 250 mg.)
Desoxycholic Acid . . . . . 50.0 mg.

DOSAGE: Two tablets with or just after meals. Dose may be reduced at discretion of physician, usually after first week.

SUPPLIED: In bottles of 84 and 500 tablets.

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Continued from page 56

LOUISIANA

Dr. Isidore Cohn, New Orleans, on the occasion of his seventieth birthday on June 12 was honored by Touro Infirmary with a reception commemorating his forty-eight years as an active member of the staff of that hospital. A bronze plaque to be installed in the outpatient clinic was unveiled and reads as follows: "1907-1955. In appreciation of forty-eight years of loyal and devoted service the Board of Managers and Medical Staff of Touro Infirmary dedicate this plaque to Dr. Isidore Cohn, physician, surgeon, teacher and friend." Dr. Cohn has been a long-time member and active in the Southern Medical Association, having served so effectively the Section on Surgery in the earlier years as its secretary, vice-chairman and chairman. He is the author of many valuable contributions published over the years in the Southern Medical Journal.

Dedication of the new 10-story addition to the Hutchinson Memorial Medical Building, which houses the school of medicine at Tulane University, New Orleans, was held Oct. 13-16. The dedication exercises were presided over by Dr. Maxwell E. Lapham, dean of the school of medicine. The principal address will be delivered by Dr. Andrew J. Warren, former director of the division of medicine and public health, Rockefeller Foundation, New York.

The nineteenth annual meeting of the New Orleans Graduate Medical Assembly will be held February 27, 28, 29 and March 1. Eighteen outstanding

Continued on page 62

TUCKER HOSPITAL, INC.

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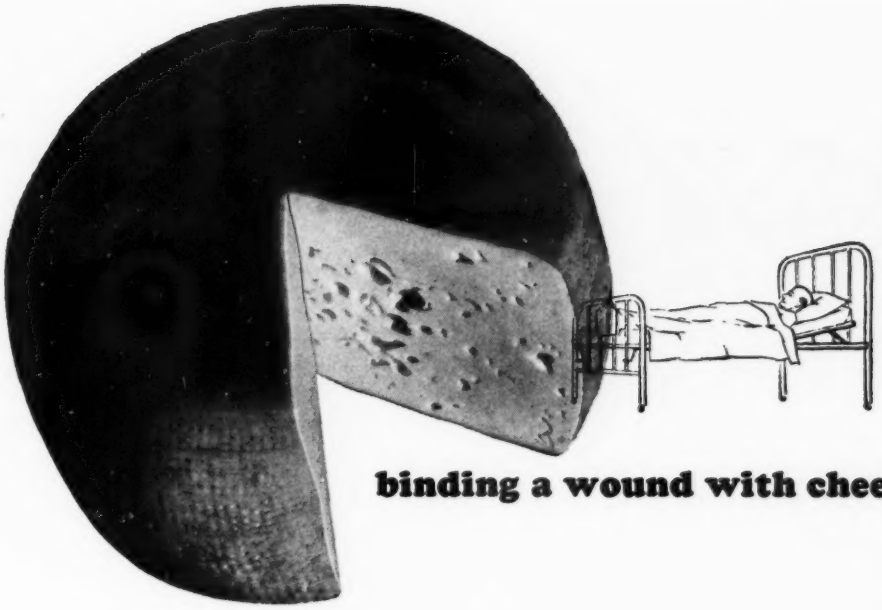
RICHMOND, VIRGINIA

This is a private hospital for the neurological practice of Drs. Beverly R. Tucker, Howard R. Masters and James Asa Shield.

The Tucker Hospital is for the treatment of nervous and endocrine diseases. There are departments of massage, medicinal exercises, hydrotherapy and physiotherapy. The Hospital is large and bright, surrounded by a lawn and shady walks, large veranda and has a roof garden. It is situated in the best part of Richmond and is thoroughly and modernly equipped. The nurses are specially trained in the care of nervous cases.



binding a wound with cheese

A wound is as strong as the connective tissue that holds it together...and the maximum strength of a wound is reached more rapidly when the diet contains liberal amounts of protein for growth of connective tissue.[1]

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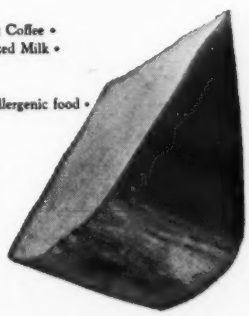
Cheese is likewise indicated for its high protein value in the geriatric diet[2] and whenever low tissue protein stores are suspected, not only in poorly healing wounds but also in patients with bed sores, chronic bullous diseases, atopic dermatitis, and senile pruritus.[3]

The wide variety of Borden cheeses lends itself to a diversified diet—from main dishes based upon popular Cheddar and Swiss or refreshing salads with soft Cottage or Cream cheese—to epicurean Camembert or Liederkranz Brand that add a tangy finish to the meal.

High palatability, pleasing texture and delicious flavor, characteristics of Borden cheeses, stimulate the appetite and contribute to greater eating enjoyment for both the convalescent and other members of the family.

Manufacturers and distributors of BORDEN'S Instant Coffee • STARLAC non-fat dry milk • BORDEN'S Evaporated Milk • Fresh Milk • Ice Cream • Cheese • EAGLE BRAND Sweetened Condensed Milk • BREMIL powdered infant food • MULL-SOY hypoallergenic food • BIOLAC infant food • DRYCO infant food • KLIM powdered whole milk

1. Babcock, C. J.: Treatment by Diet, ed. 5, Philadelphia, J.B. Lippincott Company, 1948, p. 607.
2. Sebrell, W. H., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 194.
3. Morgan, D. B.: J. Missouri M. A. 49:806 (Nov.) 1952.



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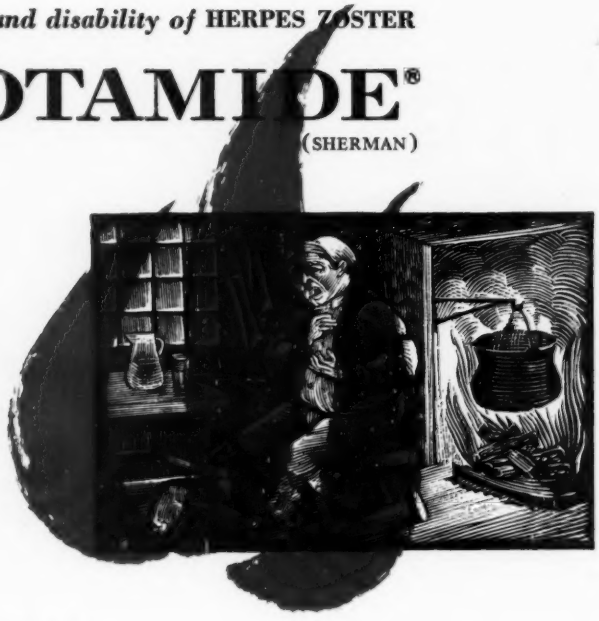

published studies show:*

Improvement is "almost immediate," with "good to excellent results" in four out of five patients, and no postherpetic neuralgia in any patient who responded favorably.

Protamide is a sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.

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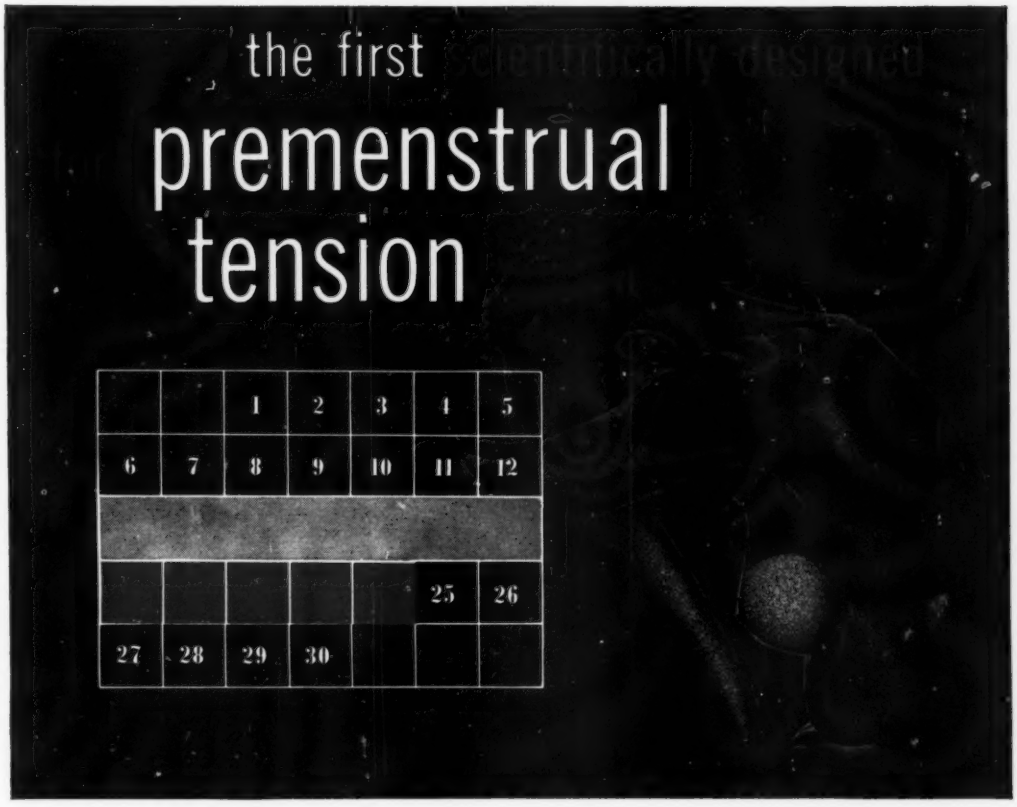
*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.



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Bickers found that "abnormal water storage can be blocked or eliminated and clinical relief of symptoms obtained in most patients . . ."[1] with NEO BROMTH.

Greenblatt recently stated: "Clinically, we share Bickers' enthusiasm for this drug in the management of premenstrual tension, especially where there is associated edema."[2]

NEO BROMTH is non-toxic, *non-hormonal* therapy and contains no ammonium chloride. Each 80 mg. tablet contains 50 mg. of pamabrom (2-amino-2-methyl-1-propanol 8 bromo-theophyllinate) and 30 mg. of pyrilamine maleate.

Dosage: 2 tablets twice daily (morning & night) beginning at onset of symptoms —usually 5 to 7 days before menses. Discontinue at onset of flow. Supplied in bottles of 100 tablets on prescription only.

1. Bickers, W.: Southern M.J., 46:873, Sept., 1953
2. Greenblatt, R.: GP, 11:66, March, 1955

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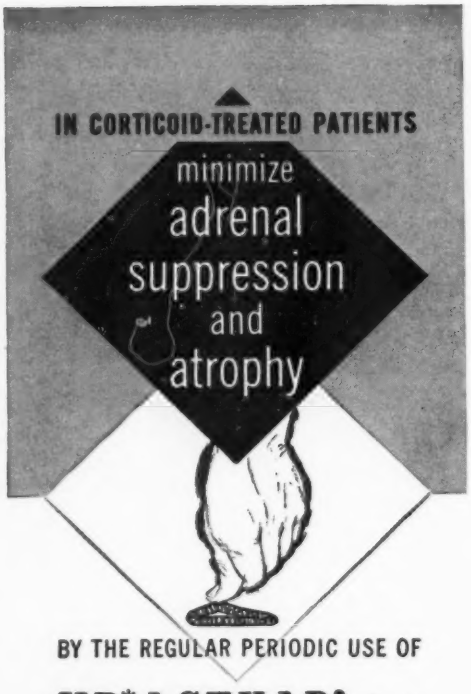

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Dosage recommendations for supportive HP*ACTHAR *Gel* are, inject:

1 a. 100 to 120 U. of HP*ACTHAR *Gel* for every 100 mg. of prednisone or prednisolone.

b. 100 U. of HP*ACTHAR *Gel* for every 200 to 300 mg. of hydrocortisone.

c. 100 U. of HP*ACTHAR *Gel* for every 400 mg. of cortisone.

2 Discontinue use of steroid on the day of injection.

*Highly Purified. HP*ACTHAR *Gel* is The Armour Laboratories brand of purified corticotropin.

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Continued from page 58

guest speakers will participate and their presentation will be of interest to both specialists and general practitioners.

Dr. Nick Accardo, New Orleans, has been named chairman of the Parochial School Health Committee; Dr. Ralph Sanchez is the assistant chairman.

Dr. Jack R. Anderson, New Orleans, was recently elected to the Council of the American Society of Ophthalmologic and Otolaryngologic.

Dr. John N. Bowden, New Orleans, was recently elected a fellow in the American College of Hospital Administrators at the annual meeting of the group.

Dr. Ambrose H. Storck was re-elected president of the Orleans Parish Unit of the American Cancer Society.

Elected to the board of directors of the Orleans Parish Unit of the American Cancer Society were: Drs. Pete Everett, A. N. Huston, Edward T. Krementz, and Robert L. Simmons.

Dr. Lawrence H. Strug, New Orleans, was recently appointed to the Advisory Board of the American Trudeau Society.

MISSISSIPPI

The University of Mississippi School of Medicine in Jackson announces the appointment of Dr. Robert D. Sloan, who has been on the staff at Johns Hopkins University School of Medicine, Baltimore, as professor of radiology and chairman of the department. Another Johns Hopkins staff member, Dr. Blair E. Batson, will become professor of pediatrics and chairman of the department in Mississippi's four-year school of medicine in the newly built University Medical Center.

MISSOURI

Dr. George E. Thoma, director of the Radioisotope Laboratory, Firmin Desloge Hospital, and instructor in internal medicine, St. Louis University School of Medicine, has been elected to the Board of Governors of the Central Society of Nuclear Medicine. His term is for three years.

A Symposium on Modern Trends in Therapy was held in St. Louis recently. The symposium was sponsored by the Lederle Laboratories Division of the American Cyanamid Company, the St. Louis Academy of General Practice, the St. Louis University School of Medicine and the Washington University School of Medicine. Dr. James W. Colbert, Jr., Dean, St. Louis University School of Medicine, moderated the morning program, while Dr. Carl Moyer, Dean of Surgery, Washington University, moderated the afternoon session.

The Missouri State Board of Medical Examiners elected the following officers for the coming year: Dr. Duff S. Allen, St. Louis, president, Dr. Harry A. Klein, St. Louis, vice-president, Dr. Elvin D. Imes, Maryville, secretary-treasurer. The other members of the board are: Dr. W. O. Pinney, Chaffee, Dr. William J. Shaw, Fayette, Dr. Edwin C. White, Kansas City, Missouri.

Continued on page 66

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rich in
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1. Grayzel, H. G., Helmer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Helmer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949.
4. Turell, R.: New York St. J. M. 50:2282, 1950.

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Propoxycaine Hydrochloride

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...prolonged anesthesia

First choice for nerve block and infiltration anesthesia

...low irritation potential

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Geriatric Vitamin-Mineral Supplement *Lederle*

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Vitamin A	5000 U.S.P. Units	Choline Dihydrogen Citrate	100 mg.	Calcium (as $CaHPO_4$)	145 mg.
Vitamin D	500 U.S.P. Units	Inositol	50 mg.	Phosphorus (as $CaHPO_4$)	110 mg.
Vitamin B_{12}	1 megm.	Ascorbic Acid (C)	50 mg.	Boron (as $Na_2B_4O_7.10H_2O$)	0.1 mg.
Thiamine Mononitrate (B_1)	5 mg.	Vitamin E (as tocopheryl acetates)	10 I. U.	Copper (as CuO)	1 mg.
Riboflavin (B_2)	5 mg.	Rutin	25 mg.	Fluorine (as CaF_2)	0.1 mg.
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Pyridoxine HCl (B_6)	0.5 mg.	Iodine (as KI)	0.5 mg.	Potassium (as K_2SO_4)	5 mg.
Ca Pantothenate	5 mg.			Zinc (as ZnO)	0.5 mg.

Other Lederle geriatric products include: GEVRABON* Vitamin-Mineral Supplement Liquid with a wine flavor; GEVRAL* Protein Vitamin-Mineral-Protein Supplement Powder; and GEVRINE* Vitamin-Mineral-Hormone Capsules.

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through vomiting or diarrhea—

Valentine's MEAT EXTRACT

stimulates the appetite,

increases the flow of digestive juices,

provides: supplementary amounts of vitamins, minerals and soluble proteins,

extra-dietary vitamin B_{12},

protective quantities of potassium, in a palatable and readily assimilated form.

Supplied in bottles of 2 or 6 fluidounces.

Dosage is 1 teaspoonful two or three times daily; two or three times this amount for potassium therapy.

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RICHMOND 9, VIRGINIA

Continued from page 62

The *Caruthersville Argus* of July 29 carried a feature article on Dr. George Wilson Phipps, Caruthersville, giving the story of his life and his fifty-six years of practice, fifty-three of them in the same office.

The National Association of Coroners at a three-day conference in August elected Dr. Hugh H. Owens, Kansas City, as president.

The Missouri Association for Retarded Children, at a two-day session in Kansas City recently, re-elected Dr. C. G. Leitch, Kansas City, as president.

Dr. Walter J. Burdette, professor and chairman, Department of Surgery, University of Missouri School of Medicine, has recently returned from Tübingen, Germany, where he engaged in investigative work in the laboratories of Professor Butenandt at the Max-Planck-Institut für Biochemie. While abroad he gave lectures at both the Universities of Heidelberg and Tübingen.

Continued on page 72

CLASSIFIED ADVERTISEMENTS

WANTED—Psychiatric residents for approved one to three year training program in affiliation with medical school. Reply: Manager, V. A. Hospital, Roanoke 17, Va.

FOR SALE—FLORIDA: Active well established $20,000 per year practice, complete with first-class laboratory, intact, as is. Includes Graduate Technician, Receptionist, Nurse, Good Will and full equipment. Ready for immediate transfer—you step in, I step out. Exceptional opportunity in community of 5000 located in ridge citrus and cattle section. Applicant must have first class references and Florida license. For further information contact SMZ c/o SMJ.

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WANTED—General Practitioner to form partnership in Eastern North Carolina. For further information contact NH c/o SMJ.

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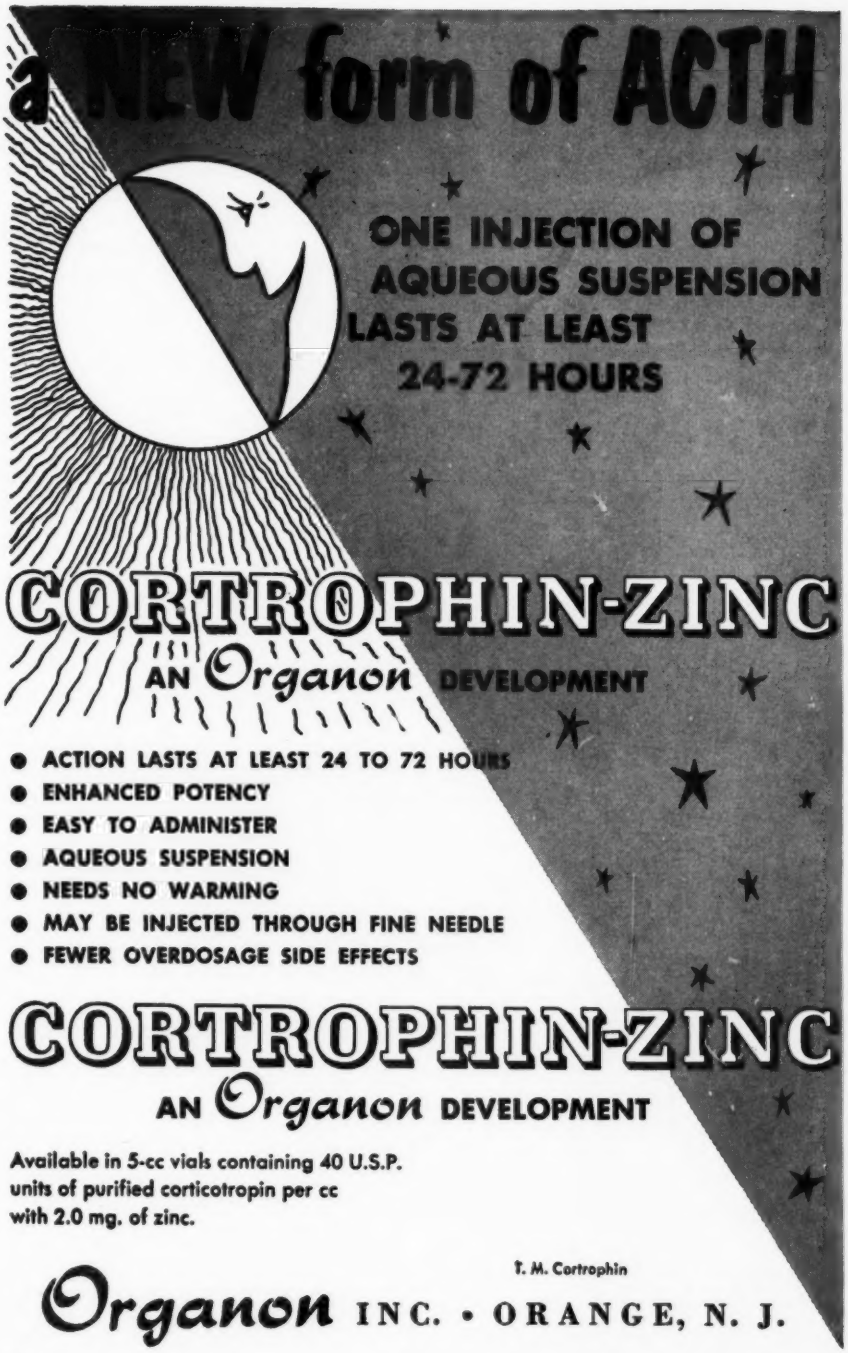
LOCATION WANTED—General Practitioner, 34 years, would like location in Texas or Oklahoma or would consider other state. Has Texas and Oklahoma license. Can furnish excellent references. Contact AE c/o SMJ.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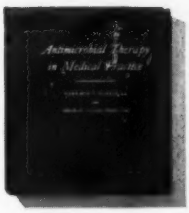
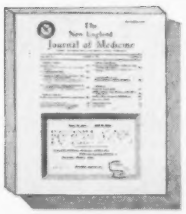


Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Co., 1955, p. 40.

Clinical studies have demonstrated rapid clinical response in cases of cystitis and pyelonephritis, including infections caused by refractory organisms.



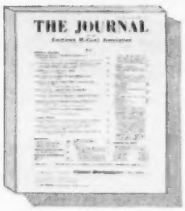
Trafton, H. M., et al.: New England J. Med. **252:** 383, 1955.

13 acute cases . . . 6 appeared cured . . . 6 markedly improved with no relapses.

36 chronic infections: 30 showed symptomatic improvement, frequently within 24 hours.

Beutner, E. H., et al.: Antibiotics Annual, 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 988.

30 chronic urinary tract infections: Of 47 strains of bacteria isolated from these patients, 29 strains (62%) were eradicated by Furadantin.



Hasen, H. B., and Moore, T. D.: J.A.M.A. **155:** 1470, 1954.

Of patients with acute urinary tract infections, 95.7% were benefited. Patients with chronic infections and those with organic or obstructive lesions were benefited in 82% of cases.

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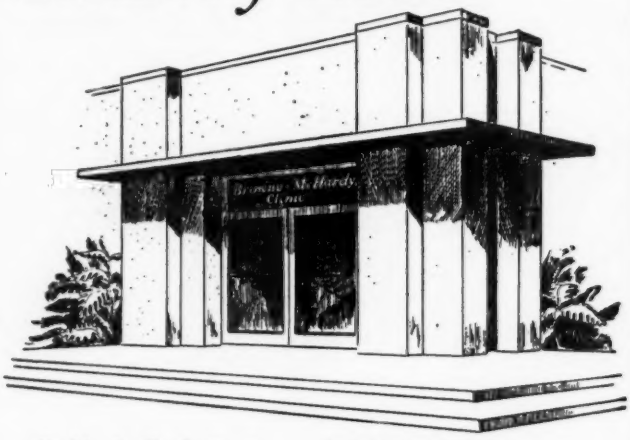

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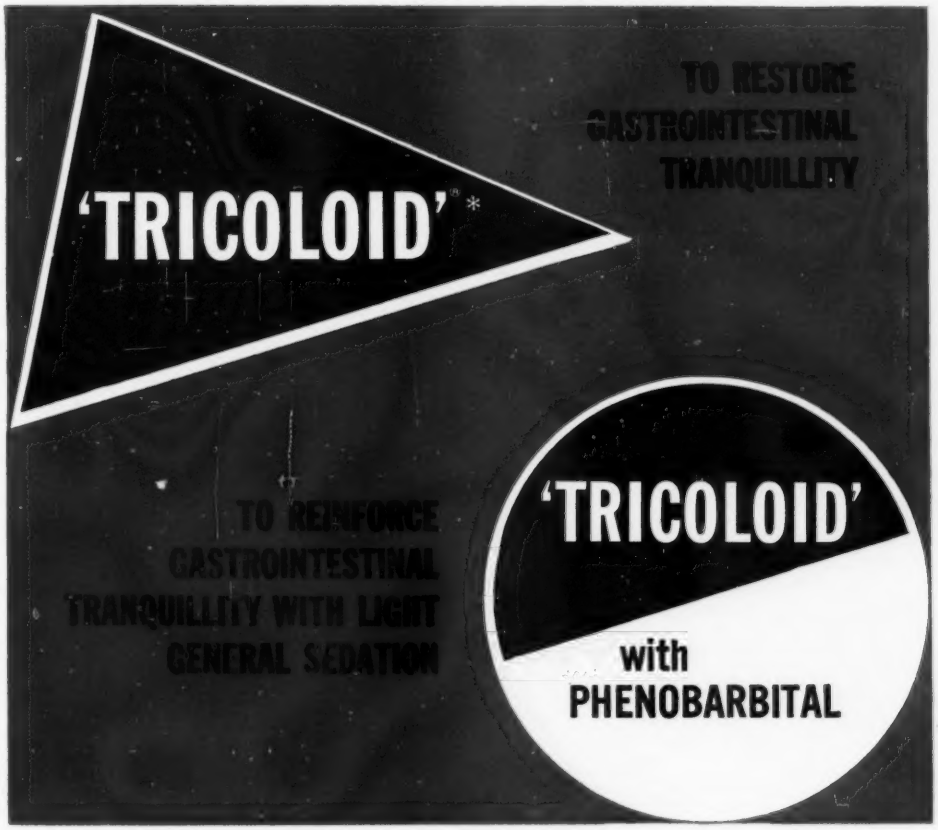

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Continued from page 66

NORTH CAROLINA

Dr. John M. Mewborn, Farmville, was elected president-elect of the North Carolina Chapter, American Association of General Practice, at the recent annual meeting. Dr. William E. Selby, Charlotte, was installed president.

Dr. G. P. Manire, an associate professor in the University of North Carolina Medical School, has been awarded a Fullbright Research Scholarship grant for the calendar year 1956. Dr. Manire has been a member of the Department of Bacteriology and Immunology since 1950.

Dr. George C. Ham, chief of psychiatric service, North Carolina Memorial Hospital, has announced the addition of twelve new psychiatric residents to the staff of the Department of Psychiatry of the University of North Carolina School of Medicine.

Duke University's million-dollar Elizabeth P. Hanes Nurses' Residence was formally dedicated at a special program on October 22.

Dr. Bayard Carter, Duke University physician, has just been honored with the presentation of his portrait to the University's Medical School. The portrait was presented by the "Nick" Carter Travel Club, a group of 48 obstetricians and gynecologists who trained at least one year under Dr. Carter, professor and chairman of the Duke Department of Obstetrics and Gynecology.

A special postgraduate course in anesthesiology was presented at Duke University, October 20-22, for North Carolina physicians. The three-day meeting was sponsored jointly by Duke and the North Carolina State Society of Anesthesiologists for doctors throughout the state who are practicing part-time anesthetists.

Dr. Ellis C. Berkowitz was appointed instructor in anatomy in the University of North Carolina School of Medicine on July 1, 1955. Dr. Berkowitz has held a position as Research Fellow at the University of California and is replacing Dr. Lionel Truscott who is now in military service.

Dr. Abraham Widra was appointed instructor in bacteriology on September 1, 1955, replacing Dr. Milton Huppert who resigned to accept a position in California. Prior to joining the University of North Carolina Medical faculty Dr. Widra was Research Associate in the Department of Bacteriology, University of Pennsylvania.

Dr. J. Norman was appointed instructor in neurologic medicine on September 1, 1955. He has had medical training at Harvard Medical School, receiving his M.D. in 1949. Dr. Allen held the position as Teaching Fellow at Harvard Medical School in 1952-53. He was Research Fellow with the Neurological Unit at Boston City Hospital in 1953-54; and Research Fellow at McLean Hospital, Waverley, Mass., from 1954-55.

The North Carolina Surgical Association held its annual fall meeting at Sea Island, Georgia, on Septem-

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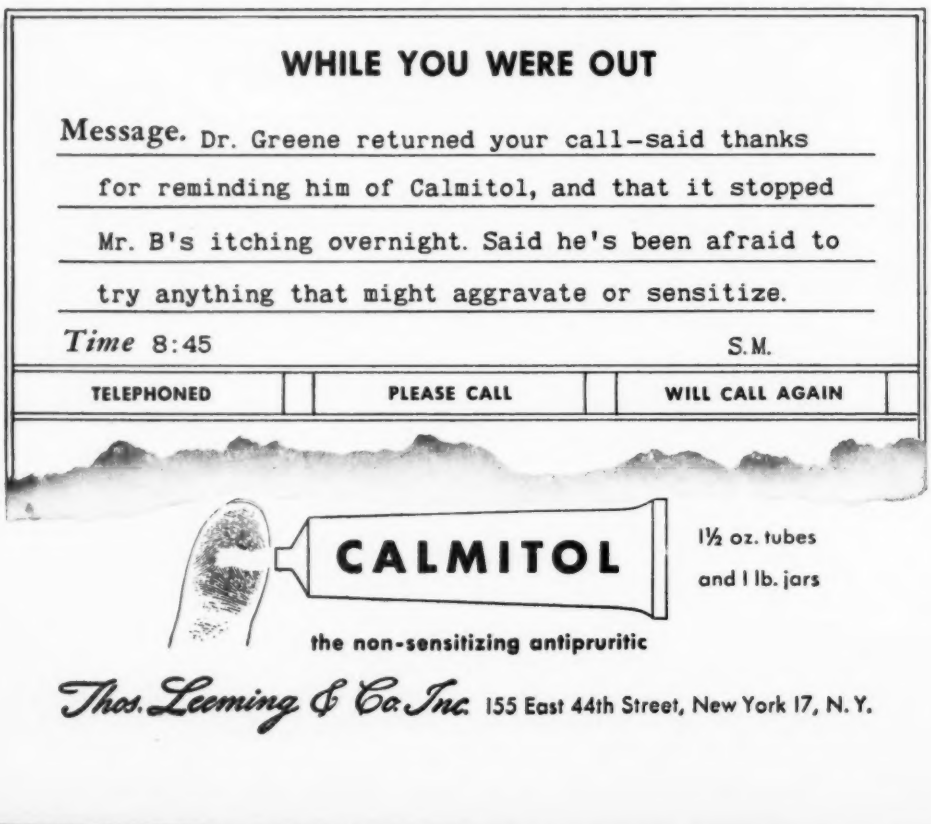
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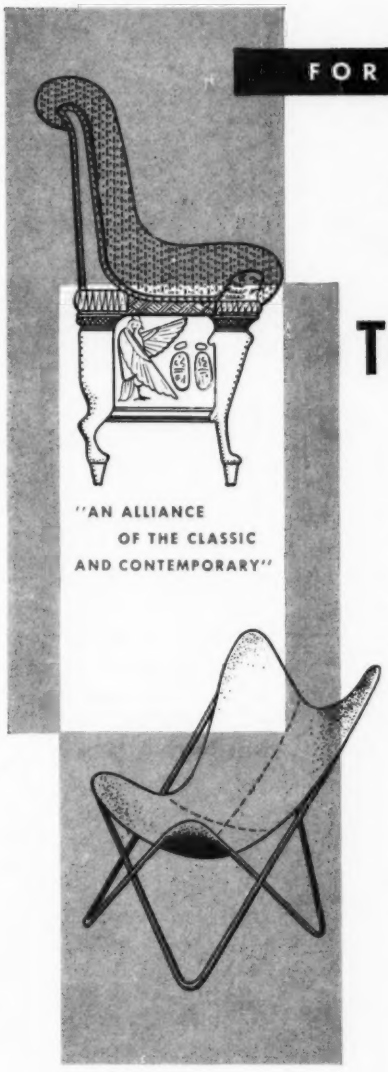

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Continued from page 72

ber 23 and 24, 1955. Officers elected were Dr. Edward W. Phifer, Morganton, president, Dr. Alexander Webb, Raleigh, president-elect, Dr. Howard Starling, Winston-Salem, vice-president, and Dr. Alfred Hamilton, Raleigh, secretary-treasurer.

Dr. Deryl Hart, professor of surgery at the Duke University School of Medicine, completed 25 years as chairman of the Department of Surgery this summer. On October 20, his former residents celebrated his twenty-fifth anniversary at a banquet, at which time his portrait was presented to the University. Dr. W. C. Davison, dean of the Duke University School of Medicine since its foundation in 1930, was the speaker.

OKLAHOMA

Dr. Charles R. Rountree, Oklahoma City, was installed as president of the Southwestern Surgical Congress at the seventh annual meeting held in early September in Kansas City, Missouri. Dr. C. M. O'Leary, also of Oklahoma City, is secretary of the group and Dr. Everett B. Neff, Oklahoma City, is Oklahoma councilor.

Dr. W. Pat Fite, Muskogee, was named president of the Board of Medical Examiners at a meeting held in Oklahoma City September 4. Other new officers are: Dr. L. S. Willour, McAlester, vice-president, and Dr. E. F. Lester, Oklahoma City, secretary. Dr. Clinton Gallaher, Shawnee, who has served as secretary for a number of years, resigned from the position. Additional members of the board are Dr. E. M. Gullatt, Ada, Dr. M. H. Newman, Shattuck, and Dr. L. E. Woods, Chickasha.

TENNESSEE

A portrait of Dr. R. Eustace Semmes, professor of neurological surgery at the University of Tennessee College of Medicine, has been presented to the University by his former residents at Baptist and John Gaston Hospitals in Memphis. Presentation was made by Dr. Francis Murphey at a luncheon honoring Dr. Semmes.

Appointment of four Memphis physicians to the staff of the University of Tennessee College of Medicine and the promotion of two others were announced recently by Dr. Frank L. Roberts, associate dean. Appointed assistants were Dr. Prentiss Truman, division of obstetrics and gynecology, Dr. Joseph H. Brock, division of surgery, and Dr. Marvin L. Wolff in the division of medicine. Dr. Louis P. Britt was appointed instructor in the Department of Orthopedic Surgery. Promoted were Dr. S. Gwin Robbins from instructor to assistant professor and Dr. Robert P. McBurney from assistant to instructor, Department of Surgery.

Dr. Norman Lee, lecturer in the Division of Chemistry at the University of Tennessee Medical Units, has been promoted to assistant professor. Dr. Lee is scientific assistant director of the Radioisotope Unit at Kennedy Veterans Hospital.

Dr. Jesse D. Perkinson, Jr., associate professor of

chemistry at the University of Tennessee Medical Units, has been awarded a $5,940 research grant by the Atomic Energy Commission. The biochemist is attempting to understand the fundamental biochemical effects of radiation, which can be applied to the clinical use of radiation.

Dr. William G. Pollard, executive director of the Oak Ridge Institute of Nuclear Studies, left in late October for a trip to Japan as the guest of the International Educational Exchange Service of the U. S. Department of State.

Dr. Robert C. Rendtorff, with the United States Public Health Service in Columbia, South Carolina, for the past three years, has joined the staff of the University of Tennessee College of Medicine as assistant professor of preventive medicine.

Four new staff members have been added to the Division of Chemistry of the University of Tennessee Medical Units, Dr. John L. Wood, chief of the division, announced. They are Dr. Robert L. Fischer of the E. I. DuPont de Nemours Laboratories at Philadelphia, Dr. William E. Jefferson, formerly connected with the Oak Ridge National Laboratories for several years, Dr. Martin Lloyd Minthorn, Jr., on the staff of the University of Illinois and Dr. Frederick W. Lengemann, who was on the staff of the University of Tennessee—Atomic Energy Commission agricultural research program at Oak Ridge, Tennessee. Dr. Fischer, Dr. Jefferson, and Dr. Lengemann will be instructors and Dr. Minthorn will be a research associate.

VIRGINIA

Dr. J. T. Showalter, Christiansburg, has been named to his second year as chairman of the blood program committee of the Roanoke Regional Red Cross Blood Center. This is a 36-chapter region in Virginia and West Virginia.

Dr. Thomas H. Jennings has been named chairman of the Recruitment Committee of the Red Cross Blood Program of Bedford County.

Dr. C. O. Finne, Slatville, has been named president of the newly organized Mountaineer Sportsmen's Association.

The Ramsey Memorial Medical Center at Gretna was dedicated in the early fall. This was built as a memorial to Dr. Oscar Lee Ramsey, Sr., who practiced there for forty-seven years before his death in 1953. The Center has facilities and equipment set up for two physicians and a dentist.

WEST VIRGINIA

The second Symposium on Coal Workers Pneumoconiosis was presented at Golden Clinic, Memorial General Hospital, Elkins, in early October. Dr. Oscar A. Sander, associate professor of medicine, Marquette University School of Medicine, Milwaukee, was the general chairman.

Dr. Frank J. Holroyd, Princeton, was re-elected AMA delegate from West Virginia for the two-year

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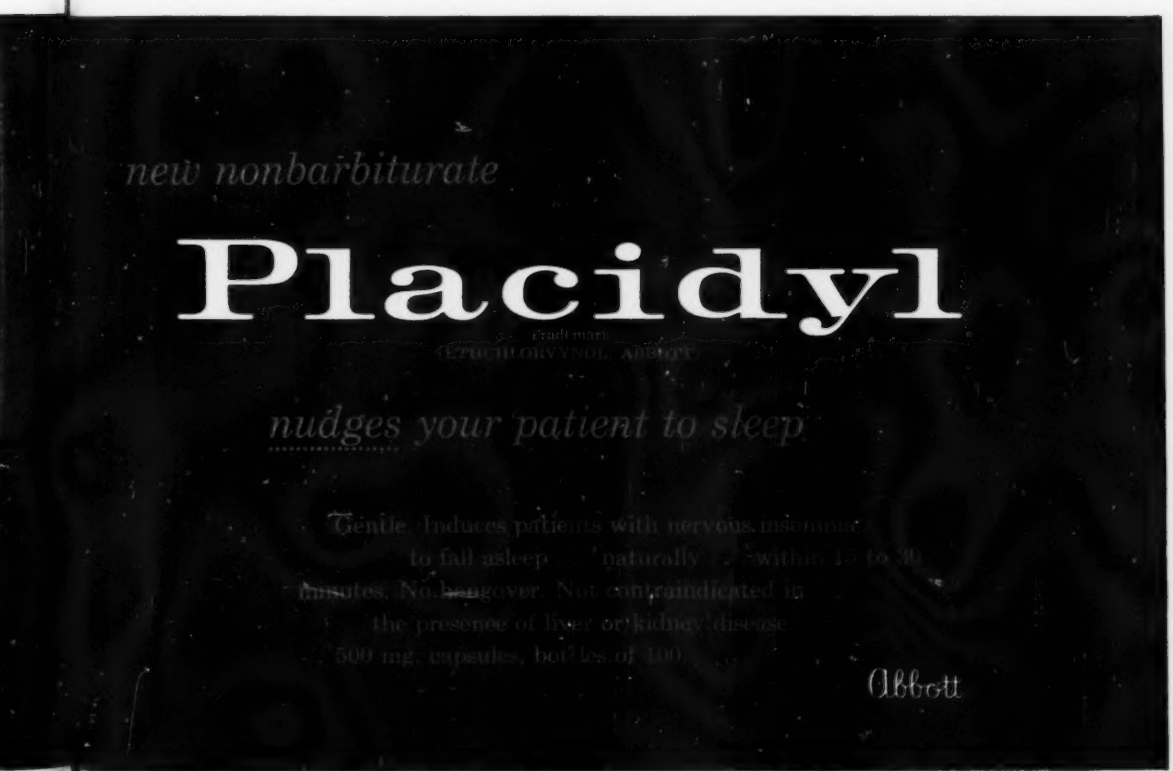

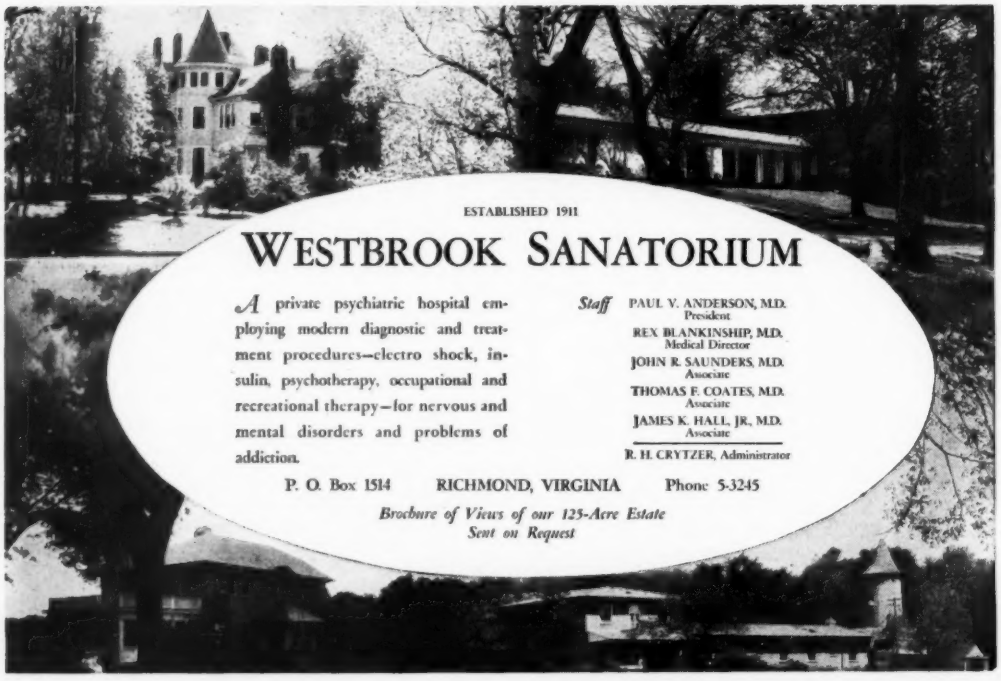

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Continued from page 77

term ending December 31, 1957. Dr. Thomas G. Reed, Charleston, was elected alternate delegate and will also serve a two-year term. Dr. Walter E. Vest, Huntington, is the other AMA delegate from West Virginia, and Dr. Jacob C. Huffman, Buckhannon, alternate AMA delegate.

Dr. George T. Evans, Fairmont, was elected president of the Alumni Association of the West Virginia University School of Medicine at the recent annual meeting at White Sulphur Springs. He succeeds Dr. Charles E. Watkins, Oak Hill. Dr. Dan N. Barber, Charleston, was named vice-president, and Dr. Clark K. Sleeth, Morgantown, secretary-treasurer.

Dr. L. F. Boland, who has practiced medicine and surgery in Mingo County for the past 30 years, has accepted appointment as medical director of the Kentucky Training Home, an institution for the care of mentally retarded children and adults, at Frankfort.

Dr. Walter G. J. Putschar, Charleston, was named president-elect of the West Virginia Association of Pathologists at the recent annual meeting. Dr. Richard C. Neale, Bluefield, was re-elected secretary-treasurer and was renamed councilor to the American Society of Clinical Pathologists. Dr. Peter Ladewig, Montgomery, was re-elected a member of the West Virginia Board of Registry.

Dr. Harry H. Howell, Madison, was re-elected president of the West Virginia Tuberculosis and Health Association at the annual meeting held in Wheeling recently.

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** Brit. Med. J. Vol. 11, No. 4839, p. 757, 1953*
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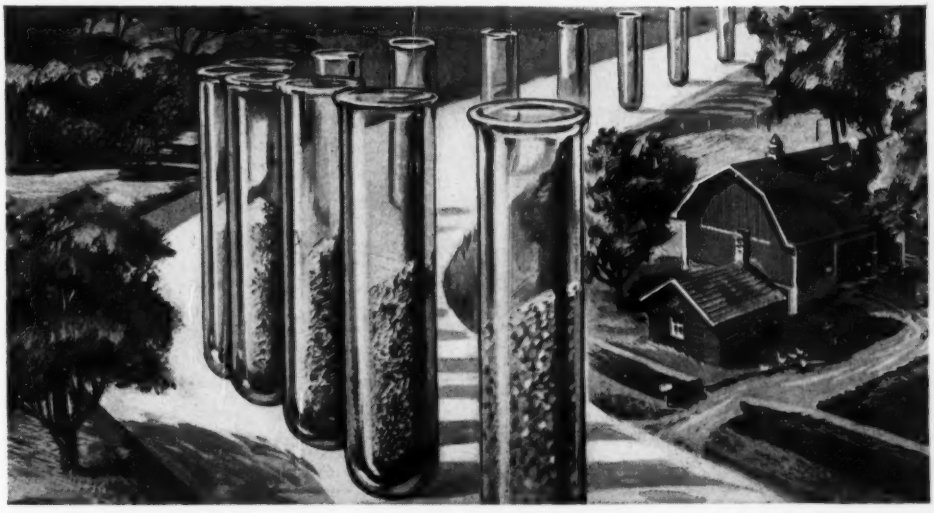
SECOND REPORT



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Dosage: Investigators of lecithin have used quantities from 7.5 to 30 grams daily in divided doses. (3 teaspoonfuls equal 7.5 grams.)

Administration: "RG" Lecithin is presented in palatable granules which may be taken plain, in milk, in orange juice or other citrus juices, or sprinkled on cereal.

Literature available on request.

Bibliography: 1. Adlersberg, D., and Sobotka, H.: J. Nutrition *25*:255 (March) 1943. • 2. Adlersberg, D., and others: Gastroenterology *10*:822 (May) 1948. • 3. Adlersberg, D.: New York J. Med. *44*:606 (March 15) 1944. • 4. Adlersberg, D., and others: Am. J. Digest. Dis. *16*:333 (Sept.) 1949. • 5. Augur, V.; Rollman, H. S., and Deuel, H. J., Jr.: J. Nutrition 33:177 (Feb.) 1947. • 6. Gross, P., and Kesten, M. B.: New York J. Med. *50*:2683 (Nov. 15) 1950. • 7. Schettler, G.: Klin. Wchnschr. *30*:627 (July) 1952. • 8. Dietrich, H. W.: South. M. J. *43*:743 (Aug.) 1950.

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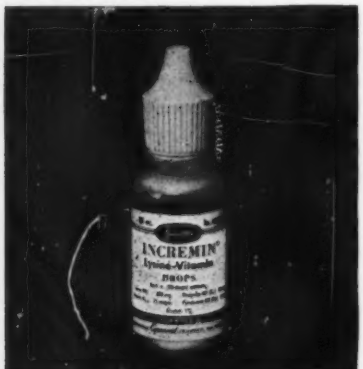

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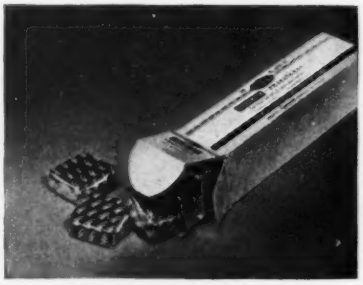

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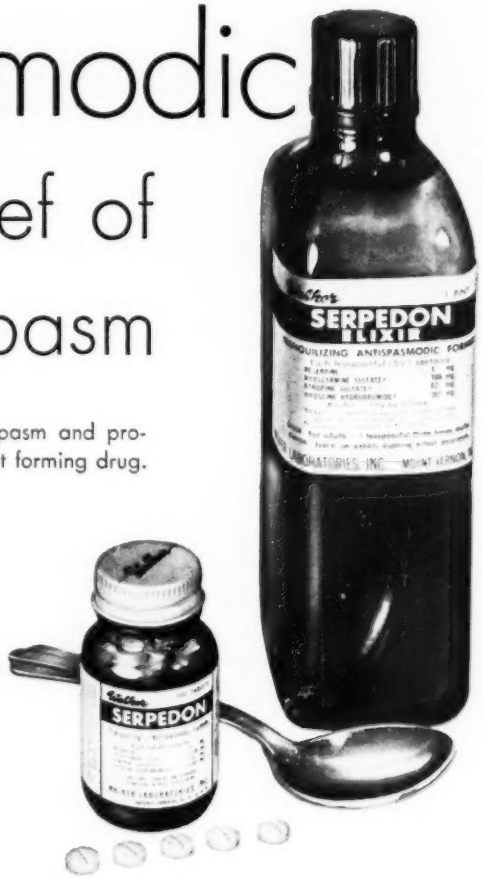

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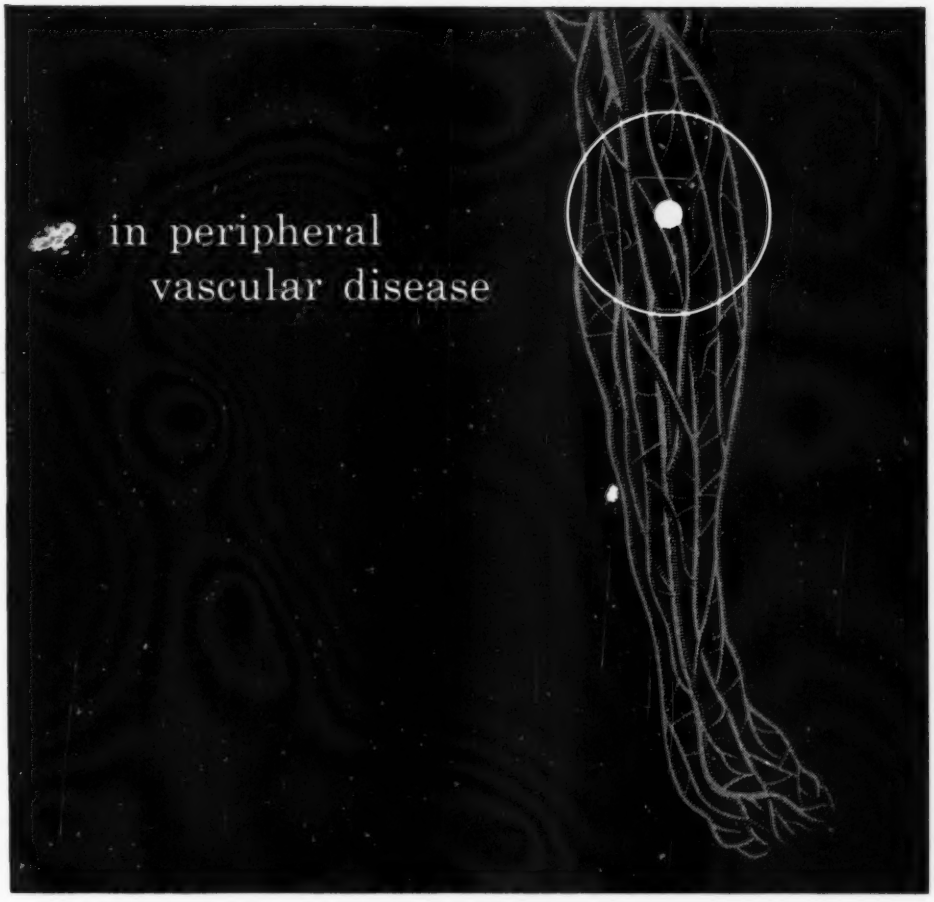

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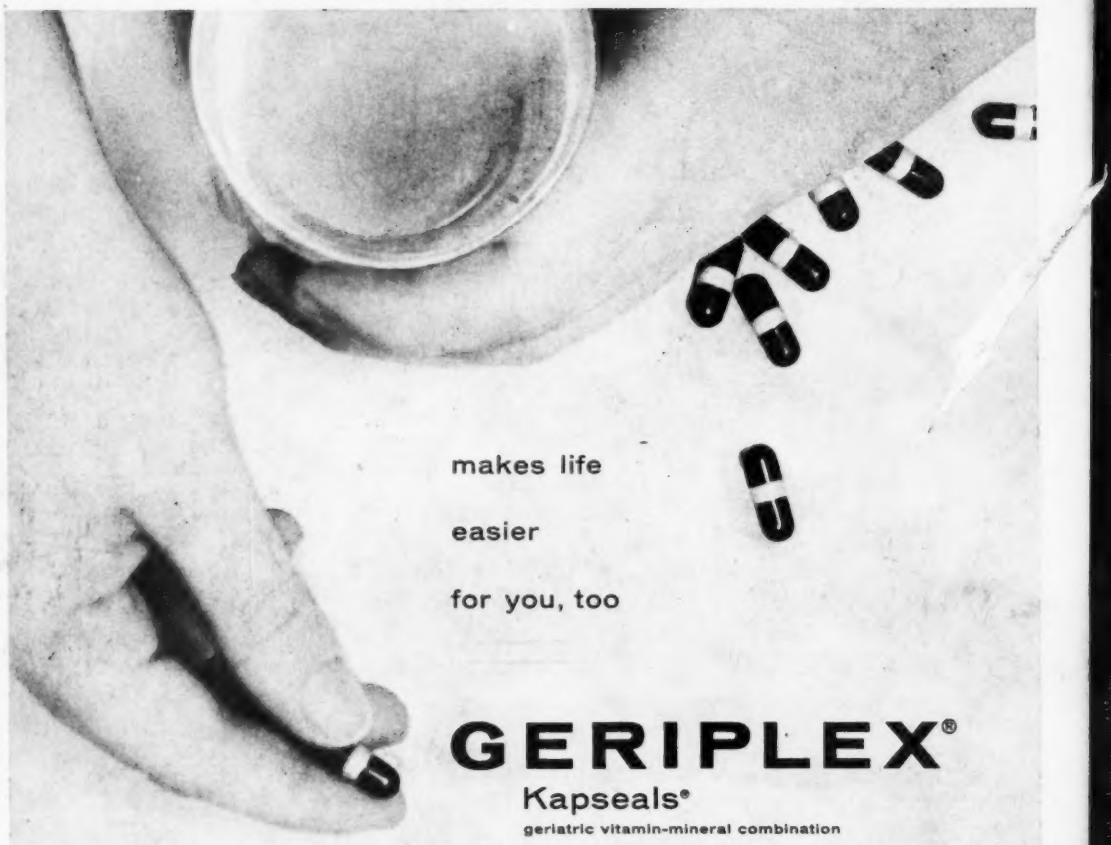

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